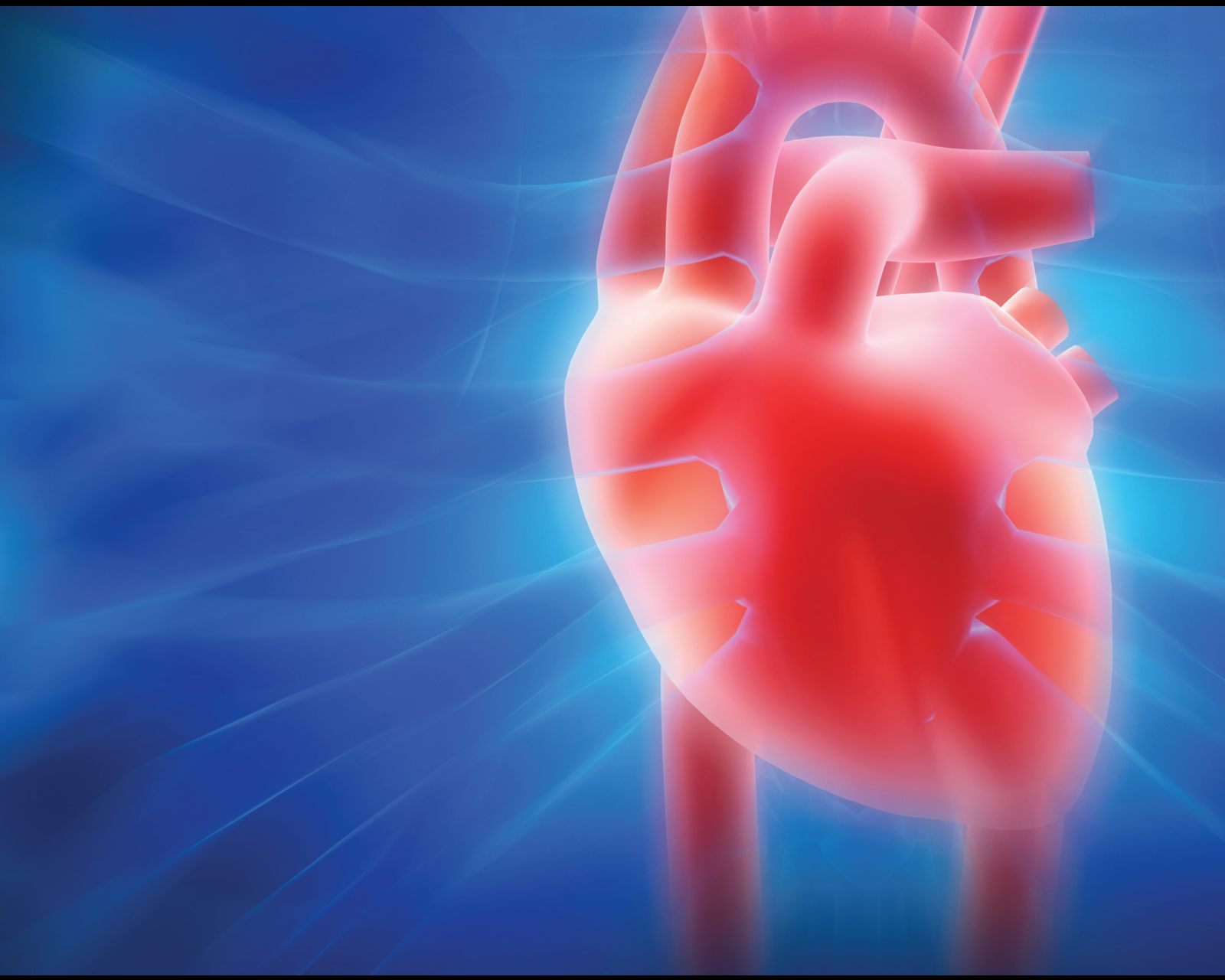
Cardiology Research and Practice

Heart Disease and Cancer: Mechanisms and Clinical Management

Lead Guest Editor: Hao Zhou
Guest Editors: Sam Toan and Nan Hu



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Retraction

Retracted: Decreased Spp1 Expression in Acute Myocardial Infarction after Ischemia and Reperfusion Injury

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We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

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[1] L. Li, J. Huang, Z. Zhao et al., "Decreased Spp1 Expression in Acute Myocardial Infarction after Ischemia and Reperfusion Injury," *Cardiology Research and Practice*, vol. 2021, Article ID 3925136, 8 pages, 2021.

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Retraction

Retracted: Verifying the Usefulness of Pulmonary Blood Flow Studies in the Correction of Pulmonary Atresia and Ventricular Septal Defect with Major Aortopulmonary Collateral Arteries

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Retraction

Retracted: Development and Validation of a Risk Prediction Model for Ventricular Arrhythmia in Elderly Patients with Coronary Heart Disease

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Retraction

Retracted: Establishment of a Nomogram for Predicting Early Death in Viral Myocarditis

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Retraction

Retracted: High-Density Lipoprotein Cholesterol in Young Nondiabetic Coronary Heart Disease Patients

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Retraction

Retracted: The Long-Term Change of Arrhythmias after Transcatheter Closure of Perimembranous Ventricular Septal Defects

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Retraction

Retracted: Clinical Study on Long-Term Sinus Reversion Rate and Left Atrial Function Recovery of Mitral Valve Disease with Atrial Fibrillation under Modified Surgical Radiofrequency Ablation

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Research Article

Value of Follow-Up N-Terminal Probrain Natriuretic Peptide (NT-proBNP) after a Modified Fontan Procedure

Jianbin Li,[1,2] **Li Ma**,[1,3] **Minghui Zou**,[1,3] **Wenlei Li**,[1,3] **Xinxin Chen**,[1,3] **Yanqin Cui**,[1,2] **and Xiaoyan Hu**[4]

[1]*Heart Center, Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, China*
[2]*Department of Paediatrics, Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, China*
[3]*Department of Cardiac Surgery, Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, China*
[4]*Department of Nursing, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, China*

Correspondence should be addressed to Li Ma; limagz@163.com and Xiaoyan Hu; 32509098@qq.com

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Objective. To assess the value of N-terminal probrain natriuretic peptide (NT-proBNP) in short-term and long-term follow-up after a modified Fontan procedure. *Methods*. We retrospectively enrolled children who had undergone a modified Fontan procedure in the Heart Center of Guangzhou Women and Children's Medical Center from January 2014 to September 2020 and collected data on NT-proBNP values before bidirectional Glenn procedure, before Fontan procedure, and on 1, 3, 7, 30, 90, and 180 days and 1, 2, 3, 4, 5, and 6 year after Fontan procedure. The relationship between changes in NT-proBNP levels and the outcomes in children was analyzed. *Results*. A total of 108 children (78 boys and 30 girls, mean age: 54.62 ± 29.38 weeks) were included in the analysis. According to one-way analysis of variance, the left ventricular type and biventricular type of single ventricle physiology showed shorter duration on cardiopulmonary bypass during the operation and lower levels of NT-proBNP after the operation than the right ventricular type and univentricular type physiology. *Conclusion*. NT-proBNP is a good indicator for mid and long-term follow-up after a modified Fontan procedure. The left ventricular type and biventricular type of single ventricle physiology show better mid and long-term benefits from the modified Fontan procedure than the right ventricular type and univentricular type physiology.

1. Introduction

The modified Fontan procedure is a final palliative procedure for treating complex congenital heart diseases such as anatomical or functional single ventricle (e.g., tricuspid atresia, mitral atresia, and hypoplastic left heart syndrome) that are not suitable for biventricular correction [1]. The Fontan operation aims to eliminate the symptoms of hypoxia and reduce the volume load of the single ventricle. It has evolved from atriopulmonary connection to total cavopulmonary connection. Moderately elevated venous pressure and sucking power of the functional ventricle are critical for patients palliated using a Fontan procedure. Abnormally increased pressure in the vena cava or decreased cardiac output can lead to chronic heart failure in patients after Fontan. Therefore, monitoring cardiac function after Fontan is of great significance to ensure good quality of life and facilitate timely intervention.

N-terminal probrain natriuretic peptide (NT-proBNP) is a marker for cardiac volume load. It is synthesized and secreted in the ventricle and released in response to the volume and pressure overload of the heart. NT-proBNP has

been demonstrated to be useful in the diagnosis and treatment of heart failure [2, 3]. However, to our knowledge, only limited data are available regarding the perioperative and postoperative values of NT-proBNP in the diagnosis of heart failure and the follow-up of outcomes. In this retrospective study of patients undergoing Fontan procedures, we investigated the changes in NT-proBNP over the perioperative period and long-term postoperative follow-up period, analyzed the relationship between NT-proBNP and echocardiographic parameters during follow-up, and discussed the value of NT-proBNP in the postoperative follow-up of cardiac function in children with single ventricle physiology.

2. Materials and Methods

This retrospective study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center. All hospitalized patients who had undergone a modified Fontan procedure (intracardiac or extracardiac conduit) with cardiopulmonary bypass in our hospital from January 2014 to September 2020 were eligible. Patients lost to follow-up were excluded. Patients were included when they had regular clinic and telephone follow-ups and had regular NT-proBNP tests and echocardiographic examinations. NT-proBNP detection principle is the electrochemiluminescence method, and we used the Roche E 601 analyzer to complete the detection. A total of 108 cases were included in the analysis. The collected clinical data included demographic features, staged anatomical features of the major blood vessels of the heart, surgical and cardiopulmonary bypass records, and follow-up data. The detailed patient data are given in Table 1.

All cases were classified into left ventricular type, right ventricular type, biventricular type, and univentricular type according to the functional ventricular morphology of congenital heart anomalies (Table 2). The classification of single ventricle was based on the findings of cardiac echo. If there were clear left and right ventricular structures and corresponding valve structures, the children were classified as biventricular type, for example, DORV and TGA/VSD/PS; if there were only fused single atrioventricular valves and the ventricles could not be distinguished, the children were classified as univentricular type. If there were mitral valve or tricuspid valve atresia or one ventricle obviously dysplasia, the patients were classified as left or right ventricular type, and the relevant statistical analysis results are given in Table 3.

During our follow-up, 1 case with right ventricular type developed progressive cardiac failure, 7 cases developed cardiac arrhythmias after surgery, including 4 patients with paroxysmal upper cardiac tachycardia, 1 patient with atrioventricular block requiring pacemaker placement, and 2 patients with ventricular arrhythmias. Significant proteinolytic enteropathy was found in 3 patients, and superior vena cava thrombosis was found in 1 patient. No pulmonary arteriovenous fistula, renal failure, and Fontan postoperative-associated liver disease were found; one patient died shortly after Fontan's operation, and no death or reoperation was found during the follow-up.

Table 1: General clinical information.

Terms	Cases
Sex (male/female)	78/30
Age at operation (weeks)	54.62 ± 29.38
Body height (cm)	97.46 ± 16.74
Body surface area (m^2)	0.67 ± 0.52
Saturation of peripheral oxygen (%)	76.33 ± 13.65
Preoperative hematocrit	47.48 ± 6.79
Proximal *M* value	2.42 ± 0.71
Distal *M* value	2.13 ± 0.65
Nakata index (mm^2/m^2)	335.9 ± 201.1
Pulmonary vascular resistance after correction (wood)	2.65 ± 1.0
18# extracardiac conduit (number of cases)	23
20# extracardiac conduit (number of cases)	59
22# extracardiac conduit (number of cases)	9
30# extracardiac conduit (number of cases)	1
Fenestration (number of cases)	101
Duration of cardiopulmonary bypass (minute)	112.77 ± 49.15
Aortic clamping (number of cases)	9
Median duration of aortic clamping (minute)	79
Duration of postoperative assisted ventilation (hour)	6
Stay in cardiac intensive care unit (day)	3
Postoperative blood oxygen saturation	90

Proximal *M* value: (proximal left pulmonary artery diameter plus proximal right pulmonary artery)/descending aorta diameter at diaphragm level. Distal *M* value: (distal left pulmonary artery diameter plus distal right pulmonary artery)/descending aorta diameter at diaphragm level.

3. Discussion

The hemodynamics after a modified Fontan procedure is considerably different from that of normal biventricular physiology, leading to markedly increased long-term mortality and dysfunction in patients who have undergone Fontan operation. It has been demonstrated that the increased mortality rate after operation is mainly caused by heart failure, arrhythmia, protein-losing enteropathy, pulmonary arteriovenous fistula, thrombosis, renal failure, and Fontan-related nephropathy; thus, many indicators have been suggested to monitor Fontan circulation during follow-up [4].

NT-proBNP, an inactive prohormone of brain natriuretic peptide, is secreted by cardiac muscle tissue in response to abnormal volume load or pressure load of the ventricle wall [5, 6]. BNP has important pathophysiological significance. It can promote the excretion of sodium and urine, has a strong vasodilator effect, and can resist the vasoconstriction of the renin angiotensin aldosterone system (RAAS) [7]. Moreover, BNP is further affected by oxidative stress and mitochondrial homeostasis/calcium homeostasis [8, 9]. It is a recognized good indicator for assessing ventricular dysfunction or heart failure. However, there are few studies on the relationship between NT-proBNP and cardiac function, outcomes, and relevant influencing factors in congenital heart disease, especially in single ventricle physiology.

A study of 77 cases by Lowenthal et al. reported the normal upper limit values of NT-proBNP in different

Table 2: The classification characteristics of patients admitted for modified Fontan procedure.

Type of single ventricle		Number of cases
Left ventricular type	Tricuspid atresia (TA)	21
	Pulmonary atresia with intact ventricular septum (PA/IVS)	2
	Pulmonary atresia with ventricular septal defect (PA/VSD)	1
	Double inlet left ventricle (DILV)	3
	Severe pulmonary stenosis (PS)	4
	Heterotaxy syndrome	1
Right ventricular type	Double inlet left ventricle (DILV)	1
	Double inlet right ventricle (DIRV)	3
	Heterotaxy syndrome	10
	Unbalanced complete atrioventricular septal defect (UBCAVC)	3
	Mitral atresia (MA)	2
Biventricular type	Transposition of the great arteries with ventricular septal defect and pulmonary stenosis (TGA/VSD/PS)	6
	Double outlet right ventricle with ventricular septal defect and pulmonary stenosis (DORV/VSD/PS)	8
	Congenitally corrected transposition of the great arteries with ventricular septal defect and pulmonary stenosis (ccTGA/VSD/PS)	10
	Congenitally corrected transposition of the great arteries with ventricular septal defect and pulmonary atresia (ccTGA/VSD/PA)	5
	Transposition of the great arteries with ventricular septal defect and pulmonary atresia (TGA/VSD/PA)	5
	Transposition of the great arteries with ventricular septal defect and pulmonary hypertension (TGA/VSD/PH)	1
	Congenitally corrected transposition of the great arteries with ventricular septal defect and pulmonary hypertension (ccTGA/VSD/PH)	1
	Double outlet right ventricle with ventricular septal defect and pulmonary hypertension (DORV/VSD/PH)	2
	Double outlet right ventricle with left ventricular outflow tract obstruction (DORV/LVOTO)	1
Univentricular type	Double inlet left ventricle (DILV)	2
	Heterotaxy syndrome	7
	Unbalanced complete atrioventricular septal defect (UBCAVC)	5
	Double inlet right ventricle (DIRV)	1
	Transposition of the great arteries with ventricular septal defect and pulmonary atresia (TGA/VSD/PA)	1

Table 3: Analysis of the difference among the patients admitted for modified Fontan procedure.

Group	Significantly different variables	Mean difference	P value
Left ventricular type vs. univentricular type	NT-proBNP level before Fontan operation	−26.41	0.015
Right ventricular type vs. biventricular type	Blood flow velocity of the left superior vena cava 1 day after operation	−0.2912	0.01
Univentricular type vs. biventricular type	Blood flow velocity of the left superior vena cava on postoperative day 1	−0.2428	0.049
Left ventricular type vs. univentricular type	Blood flow velocity at the anastomosis of the pulmonary artery and conduit on postoperative day 1	−0.104	0.002
Right ventricular type vs. biventricular type	Blood flow velocity at the anastomosis of the pulmonary artery and conduit on postoperative day 1	−0.151	0.00
Right ventricular type vs. biventricular type	Blood flow velocity of the left superior vena cava 6 months after the operation	−0.16	0.017
Right ventricular type vs. left ventricular type	Blood flow velocity of the inferior vena cava 1 year after the operation	−0.075	0.019
Left ventricular type vs. right ventricular type	Valve reflux 1 year after the operation	−0.845	0.02
Left ventricular type vs. right ventricular type	Blood flow velocity of the right superior vena cava 2 years after the operation	−0.116	0.022

Table 3: Continued.

Group	Significantly different variables	Mean difference	P value
Right ventricular type vs. biventricular type	Blood flow velocity of the inferior vena cava 2 years after the operation	−0.082	0.03
Right ventricular type vs. biventricular type	Blood flow velocity of the right superior vena cava 3 years after the operation	−0.089	0.034
Left ventricular type vs. biventricular type	Blood flow velocity of the inferior vena cava 3 years after the operation	−0.078	0.016
Left ventricular type vs. right ventricular type	Blood flow velocity of the right superior vena cava 4 years after the operation	0.17	0.014
Left ventricular type vs. right ventricular type	Blood flow velocity at the anastomosis of the pulmonary artery and conduit 4 years after the operation	0.26	0.00
Left ventricular type vs. univentricular type	Blood flow velocity at the anastomosis of the pulmonary artery and conduit 4 years after the operation	0.23	0.00
Left ventricular type vs. biventricular type	Blood flow velocity at the anastomosis of the pulmonary artery and conduit 4 years after the operation	0.11	0.001
Univentricular type vs. biventricular type	Blood flow velocity at the anastomosis of the pulmonary artery and conduit 4 years after the operation	−0.11	0.002
Right ventricular type vs. left ventricular type	NT-proBNP level 7 days after the operation	1143.95	0.003
Right ventricular type vs. biventricular type	NT-proBNP level 7 days after the operation	1007.51	0.007
Right ventricular type vs. univentricular type	NT-proBNP level 7 days after the operation	942.29	0.038
Right ventricular type vs. biventricular type	NT-proBNP level 30 days after the operation	42.96	0.023
Left ventricular type vs. right ventricular type	NT-proBNP level 180 days after the operation	−872.59	0.001
Right ventricular type vs. univentricular type	NT-proBNP level 180 days after the operation	857.032	0.014
Right ventricular type vs. univentricular type	NT-proBNP level 180 days after the operation	1008.84	0.000
Left ventricular type vs. right ventricular type	Duration of cardiopulmonary bypass	−27.01	0.049
Left ventricular type vs. univentricular type	Duration of cardiopulmonary bypass	−47.34	0.001
Univentricular type vs. biventricular type	Duration of cardiopulmonary bypass	49.08	0.001
Right ventricular type vs. biventricular type	Duration of cardiopulmonary bypass	28.74	0.032
Left ventricular type vs. univentricular type	Duration of aortic clamping	−29.19	0.002
Right ventricular type vs. univentricular type	Duration of aortic clamping	−20.18	0.043
Univentricular type vs. biventricular type	Duration of aortic clamping	27.26	0.002
Left ventricular type vs. univentricular type	Blood oxygen saturation at discharge	15.17	0.019
Univentricular type vs. biventricular type	Blood oxygen saturation at discharge	−13.99	0.033

palliation stages of single ventricle physiology: 300 pg/mL after a Blalock–Taussig shunt or pulmonary banding, 1100 pg/mL after bidirectional Glenn operation, and 1900 pg/mL after Fontan operation. The researchers noted that NT-proBNP is a sensitive and effective tool to evaluate cardiac function changes after Fontan operation.

With a larger number of cases, our study showed a good correlation between NT-proBNP and mid and long-term cardiac functions after a modified Fontan procedure. The changes in NT-proBNP levels showed high sensitivity in reflecting the changes in cardiac function of children, especially in those with postoperative valve reflux, arrhythmia, and residual pulmonary venous obstruction, whose NT-proBNP levels were significantly increased. Our results were consistent with Chen's findings that severe valve reflux and pulmonary arterial pressure of >15 mmHg are risk factors for heart failure and show poor outcome after a modified Fontan procedure [10, 11].

Comparison of the mid and long-term post-Fontan outcomes between different types of single ventricle

physiology in our study showed that cases of left ventricular type had a relatively good long-term prognosis, and surprisingly, cases of biventricular type showed relatively good mid and long-term outcomes after Fontan operation, who would, in theory, be expected to benefit more from biventricular correction. However, prior to our study, there has been little research about the mid and long-term outcomes after modified Fontan operation in complex congenital heart disease such as double outlet right ventricle with noncommitted ventricular septal defect. The significant differences in cardiopulmonary bypass time during operation, blood oxygen saturation after operation, and NT-proBNP levels at 7 days, 30 days, and 180 days after operation indicated that left ventricular type and biventricular type physiology were associated with shorter operation time, more rapid recovery of cardiac function, and more normal blood oxygen saturation after a modified Fontan procedure than univentricular type and right ventricular type physiology. The possible reason for the poor prognosis in the right ventricular group was that the right ventricular structure and tricuspid valve could not tolerate the high afterload of systemic circulation for a long time, leading to the symptoms of gradually worsening heart failure.

There were no significant differences between left ventricular type and biventricular type with respect to echocardiographic results and NT-proBNP values after Fontan operation, suggesting no significant difference in mid and long-term outcomes between the two types of single ventricle physiology. The possible reason for the difference of blood flow velocity in upper and lower lumens after modified Fontan is that the abnormal increase of pulmonary circulation resistance causes the obstruction of blood flow in upper and lower lumens, and the decline of ventricular diastolic function and valve regurgitation are the main reasons for the increase of pulmonary circulation resistance. However, this finding is limited by the small number of patients in this study, and hence, more cases should be enrolled and analyzed in future studies to validate and improve this research.

4. Conclusion

This mid and long-term follow-up study found that NT-proBNP is a sensitive and reliable indicator to evaluate cardiac function after a modified Fontan procedure. The left ventricular type and biventricular type of single ventricle physiology show better outcomes after operation in terms of valve reflux, blood oxygen saturation, and blood flow velocity of the superior and inferior vena cava than the right ventricular type and univentricular type.

Data Availability

The raw clinical data cannot be provided due to privacy concerns, but will have the data available once permission is obtained from the corresponding author or institution.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Retraction

Retracted: Decreased Spp1 Expression in Acute Myocardial Infarction after Ischemia and Reperfusion Injury

Cardiology Research and Practice

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] L. Li, J. Huang, Z. Zhao et al., "Decreased Spp1 Expression in Acute Myocardial Infarction after Ischemia and Reperfusion Injury," *Cardiology Research and Practice*, vol. 2021, Article ID 3925136, 8 pages, 2021.

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Research Article

Decreased Spp1 Expression in Acute Myocardial Infarction after Ischemia and Reperfusion Injury

Ling Li, Jungang Huang, Zongkai Zhao, Zhuzhi Wen, Kang Li, Tianjiao Ma, Lisui Zhang, Junmeng Zheng, and Shi Liang

Department of Cardiovascular Surgery, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou 510120, China

Correspondence should be addressed to Junmeng Zheng; zhengjm27@mail.sysu.edu.cn and Shi Liang; md02ls@mail2.sysu.edu.cn

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Background. With the progress of shock therapy and the establishment and promotion of methods such as thrombolytic therapy and percutaneous coronary intervention (PCI), many tissues and organs have been reperfused after ischemia which may cause even worse disorder called ischemia-reperfusion injury (IRI). mRNAs have been found to have significant impacts on ischemia-reperfusion through various mechanisms. In view of the accessibility of mRNAs from blood, we aimed to find the association between mRNA and ischemia-reperfusion. *Methods*. We used the GSE83472 dataset from the Gene Expression Omnibus (GEO) database to find differential RNA expression between ischemia-reperfusion tissue and control samples. In addition, Gene Ontology (GO) annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses were performed to find the biological property of 449 RNAs from GSE83472 via the Database for Annotation, Visualization, and Integrated Discovery (DAVID). Besides, Gene Set Enrichment Analysis (GSEA), a tool to find the pathway orientation of a gene set, was used for further study in the four most significant KEGG pathways. Furthermore, we constructed a protein-protein interaction (PPI) network. In the end, we used quantitative reverse transcription-polymerase chain reaction (qRT-PCR) and western blotting to measure and compare the expression of Spp1 in patients who accepted percutaneous coronary intervention. *Results*. The bioinformatics analyses suggested that Spp1 was a hub gene in reperfusion after ischemia. The qRT-PCR result showed that the Spp1 expression was significantly downregulated in ischemia-reperfusion cells after PCI compared with normal samples and so as the western blotting. *Conclusion*. Spp1 might play an essential role in acute myocardial infarction after ischemia and reperfusion injury.

1. Introduction

Myocardial infarction (MI) ranks first among the heart vascular events around the world; the timely and effective recovery of coronary artery blood flow is an effective method for the treatment of ischemic heart disease [1]. However, the process of blood reperfusion may cause myocardial tissue structure, energy metabolism, electrophysiology, and heart function damage; this phenomenon is called myocardial ischemia-reperfusion [2]. The underlying mechanism is various. The accumulation of lactate, protons, and NAD+ in ischemic tissue causes the decrease of pH. The H+ ions were extruded in exchange for Na+ through the Na^+/H^+ exchanger. Consequently, the cell extrudes Na^+ in exchange for Ca^{2+} by the Na^+/Ca^{2+} exchanger. The surplus Ca^{2+}, flowing into the mitochondria, may activate the Ca^{2+}/calmodulin-dependent protein kinases pathologically [3]. A recent study considered that the IRI promoted the production of proinflammatory cytokines and induced proapoptotic pathways of the unfolded protein response (UPR) [4]. Secreted phosphoprotein-1 (Spp1), also called as osteopontin (OPN), is a protein secreted by the SPPL gene encoded on human chromosome 4q22.1 which interacts with a number of adhesion receptor-binding motifs including a C-terminal CD44v6 domain and thrombin-cleaved N-terminal integrin domain [5]. Recent studies show that Spp1 is an extracellular matrix protein closely related to tumors, which is expressed at a high level in many tumors and involved in the regulation of tumor invasion, metastasis, apoptosis inhibition, and angiogenesis [6]. In our study, differentially expressed RNAs

(DE-RNAs) were identified from the GSE83472 dataset, and we found Spp1 as the candidate associated with IRI. Then, we analyzed the functional enrichment of specific biologic processes via DAVID. A PPI network was generated and measured for finding the hub gene associated with IRI. Finally, we validated the downregulation of Spp1 expression in ischemia-reperfusion patients after PCI.

2. Methods

2.1. Data Download and Clinical Samples. We obtained the GSE83472 dataset from GEO (http://www.ncbi.nlm.nih.gov/geo/) [7]. The GSE83472 dataset, including 8 mouse SHAM (4 WT and 4 AKIP_TG) and 8 mouse IR (4 WT and 4 AKIP1_TG) where ischemia/reperfusion injured, was used to identify differential gene expression for mice with I/R injury. Meanwhile, we gathered clinical samples from 9 males and 7 females, with an average age of 53.6 ± 8.4 years, who accepted percutaneous coronary intervention because of acute myocardial infarction from 2018 to 2020. The whole blood samples from patients and healthy people were gathered. The guidelines of the Ethics Committee of Sun Yat-sen University, Sun Yat-sen Memorial Hospital (SYSEC-KY-KS-2021-070), were obeyed.

2.2. Data Processing. We used the R language and applied the R package of "limma" to process the GSE83472 RAW dataset ($p < 0.05$). Then, we screened out DE-RNAs according to the criteria gene expression values. Furthermore, we made volcano plot and heat map for differential expression genes and the analysis results.

2.3. GO Functional Annotation and KEGG Pathway Enrichment Analysis. To analyze GO terms of DE-RNAs and the enrichment in KEGG pathways, we used DAVID to reveal potential functions and the biological property of DE-RNAs with $p < 0.05$ [8].

2.4. GESA. For further study, GESA, a tool for learning the enrichment in specific functional gene sets, was performed using the online tool available at http://software.broadinstitute.org/gsea. The gene sets of C2 (curated) KEGG, C5 (GO) cellular components, C5 (GO) biological processes, and C5 (GO) molecular functions were used to find the function of DE-RNAs through the R package cluster Profiler [9].

2.5. PPI Network Construction. To explore the association of DE-RNAs, we subsequently generated the PPI biological network and evaluated the interaction through the STRING database (https://string-db.org/). In addition, Cytoscape software was used for the visualization of interactions and finding the hub gene in functional networks [10]. Finally, the hub genes were verified by the MCODE method, and the CytoHubba application was used to rank the gene and construct a network by its score [11].

2.6. qRT-PCR Analysis. We synthesized cDNA by reverse-transcribing RNA by using RNA Transcription Kit (Western Biotech, Chongqing, China). The forward primers and reverse primers are listed in Table 1. Then, we used SYBR Green Mix (Yeasen Biotech Co., Ltd.) to perform qRT-PCR on a Roche Real-Time PCR System according to the manufacturer's instructions. We calculated fold changes in RNA expression using the $2^{-\Delta Ct}$ ($2^{-[(Ct \text{ of gene})-(Ct \text{ of U6})]}$) method as previously described [12].

2.7. Western Blotting Assay. Cells were collected and resolved on ice with RIPA buffer. After that, the protein samples were separated in 10% polyacrylamide SDS-PAGE and transferred onto a polyvinylidene fluoride (PVDF) membrane [13]. After transferring, we blocked the PVDF membranes with 5% bovine serum albumin (BSA). We used osteopontin (Abcam, ab166709) and GAPDH (Cell Signaling Technology) as primary antibodies to incubate blocked membranes at 4°C overnight and horseradish peroxidase as the secondary antibody at room temperature. Finally, samples were detected by using the ECL detection kit (Yeasen Biotech Co., Ltd.) [14].

2.8. Statistical Analysis. For the qRT-PCR in clinical samples, Student's *t*-test was performed using GraphPad 7.0. We used R software (https://www.r-project.org/) to perform bioinformatics analysis. The values were shown as mean ± standard deviation and then analyzed using two-tailed Student's *t*-tests. A p value of <0.05 was considered to indicate a statistically significant difference.

3. Results

3.1. Bioinformation Analysis from the GSE83472 Dataset. We screened out DE-RNAs according to the criteria that $|\text{Log2FC}| > 1$, where FC represented fold change, and p value <0.05. Subsequently, 221 upregulated DE-RNAs and 318 downregulated DE-RNAs were identified. The result was shown in the volcano plot and heat map, respectively (Figures 1(a) and 1(b)). To identify the function of target genes, we utilized DAVID to perform GO annotation and KEGG pathway analyses. The top 4 significant GO terms and KEGG pathways are shown in Figures 1(c)–1(f). The significantly enriched entries for the biological process were the negative regulation of the apoptotic process (Figures 1(c)–1(f)). The most enriched cellular component was functions in the cytoplasm (Figure 1(d)), and protein binding was dominant in the molecular function (Figure 1(e)).

3.2. Enrichment Analysis by GSEA. GSEA was performed to evaluate the GO gene sets and KEGG signaling pathway gene sets between IR and NIR. Twenty signaling pathways were differentially enriched, among which the largest enrichment score (ES) was propanoate metabolism, valine, leucine, and isoleucine degradation, Parkinson's disease, citrate cycle (TCA cycle), mitochondrial respiratory chain

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Table 1: Primers.

SPP1	Forward	CTCCATTGACTCGAACGACTC
	Reverse	CAGGTCTGCGAAACTTCTTAGAT
GAPDH	Forward	ACAACTTTGGTATCGTGGAAGG
	Reverse	GCCATCACGCCACAGTTTC

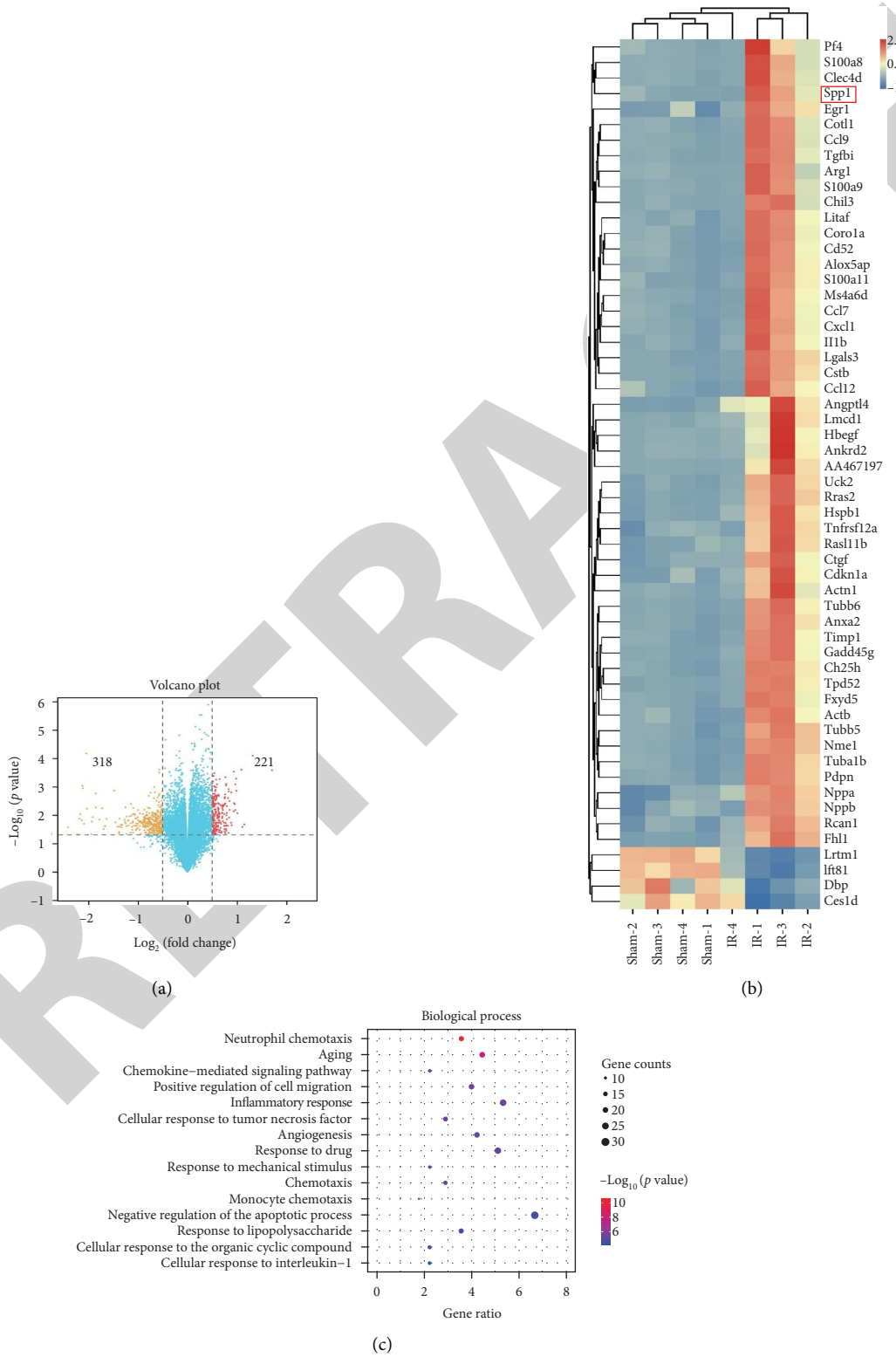

Figure 1: Continued.

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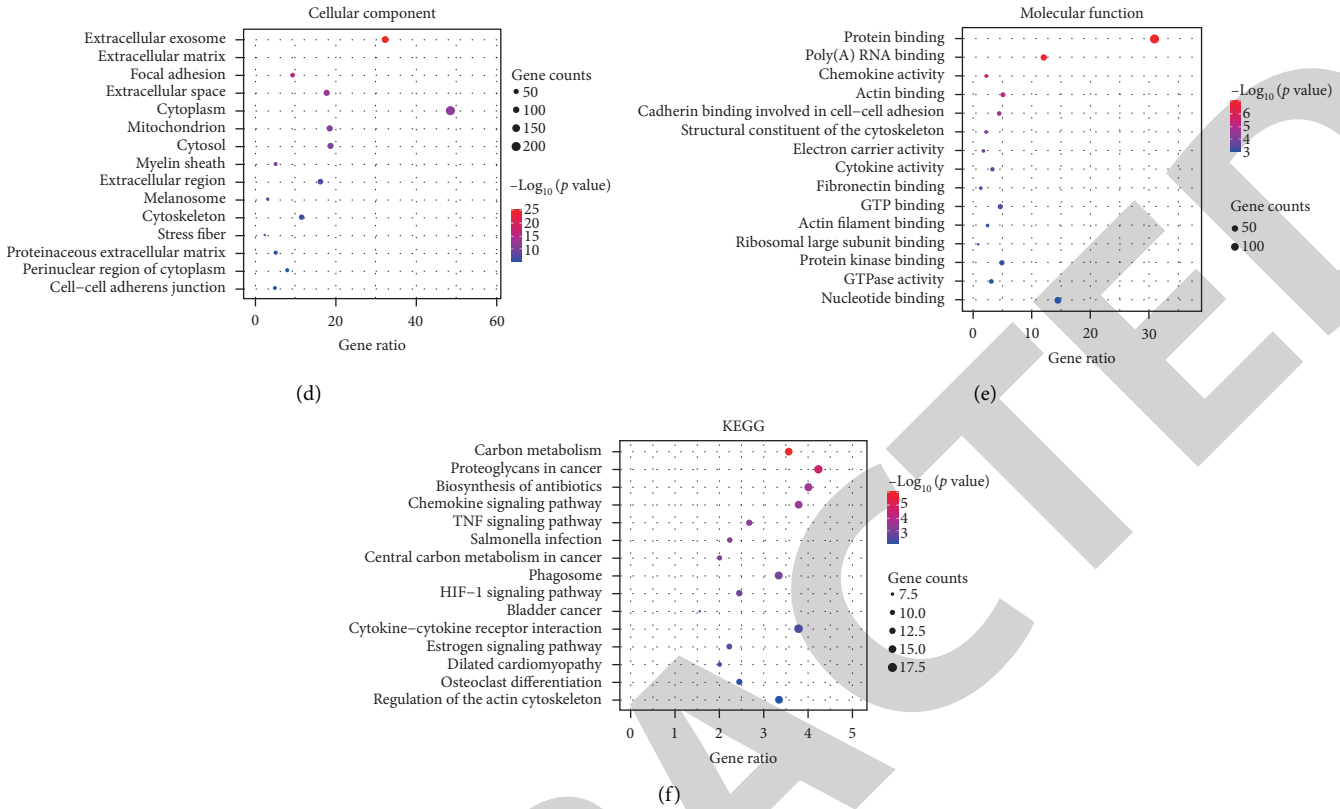

Figure 1: Bioinformation analysis from the GSE83472 dataset. (a) Volcano plot of DE-RNAs from the GSE83472 dataset. Red dot represented upregulated RNAs, and yellow dot represented downregulated RNAs. (b) Heat map of hierarchical clustering analysis for DE-RNA expression. Red represented greater expression, and blue represented less expression. (c–f) The top 15 significant KEGG pathways and GO terms related to the biological process, cellular component, molecular function.

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complex 1 biogenesis, mitochondrial respiratory chain complex assembly, fatty acid beta oxidation using acyl-CoA dehydrogenase, mitochondrial ATP synthesis coupled proton transport, NADH dehydrogenase complex, proton-transporting ATP synthase complex, respiratory chain, inner mitochondrial membrane protein complex, oxidoreductase activity acting on NADPH quinone or similar compound as the acceptor, acyl-CoA dehydrogenase activity, NAD-ADP ribosyl transferase activity, and oxidoreductase activity acting on NADPH (Figures 2(a) and 2(c)–2(e)), and the largest negative enrichment score (NES) was ribosome, NOD-like receptor signaling pathway, DNA sensing pathway, and pathogenic *Escherichia coli* infection (Figure 2(b)).

3.3. Spp1 Was Identified as the Hub Gene Associated with Ischemia, Cell Injury, and Inflammation. A PPI network including 400 nodes and 2085 edges with association confidence score >0.4 was constructed to distinguish the connection among 539 DE-RNAs by the STRING database. Within the 26 genes identified by the MCODE application, the Spp1 gene had a high score (Figure 3(a)). As shown in the figure, the hub gene network and functional clustering indicated Spp1 as the hub gene associated with IRI (Figures 3(b) and 3(c)).

3.4. Spp1 Was Downregulated in Ischemia-Reperfusion Samples after PCI. We quantified the expression levels of Spp1 by qRT-PCR in the whole blood cells (Figure 4(a)). The expression of Spp1 in ischemia-reperfusion samples after PCI was significantly decreased compared to the control. The western blotting result indicated the downregulation of Spp1 expression in ischemia-reperfusion samples at the protein level (Figure 4(b)).

4. Discussion

Tissue lesion caused by ischemia is the main cause of fatal diseases, such as MI and stroke [15]. MI can lead to the gradual development of heart failure, chronic ischemic heart disease, the result of persistent or repeated aggravation of myocardial ischemia, and hypoxia caused by severe coronary artery atherosclerotic stenosis [16]. In gross appearance, the thickness of the heart wall may be normal, with multifocal white fibrous bands or transmural scars. The endocardium thickens and loses its normal luster and sometimes with mural thrombus. In addition, MI can induce multifocal myocardial fibrosis and myocardial fiber hypertrophy. During the rescue and treatment of ischemic diseases, scientists gradually discovered that the main lesion to tissues is not the ischemia itself, but after the blood supply is restored, excessive free radicals attack

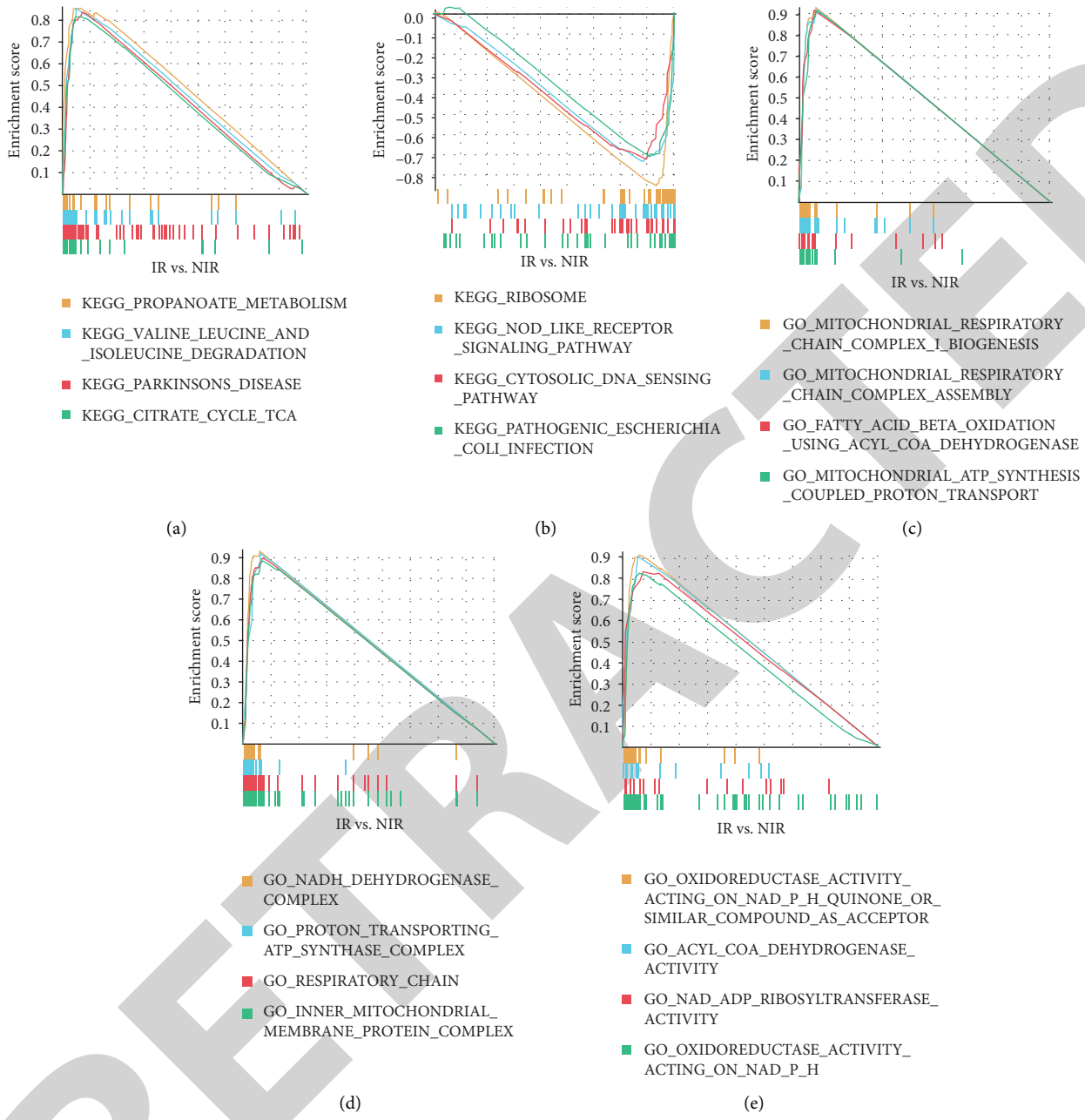

Figure 2: Enrichment analysis by GSEA. (a) In gene sets of KEGG, GSEA revealed that the genes of IR were mainly enriched in propanoate metabolism, valine, leucine, and isoleucine degradation, Parkinson's disease, and citrate cycle (TCA cycle). (b) In gene sets of KEGG, GSEA revealed that the genes of IR were mainly negatively enriched in ribosome, NOD-like receptor signaling pathway, DNA sensing pathway, and pathogenic *Escherichia coli* infection. (c–e) In gene sets of GO, GSEA revealed that the genes of IR were mainly enriched in mitochondrial respiratory chain complex 1 biogenesis, mitochondrial respiratory chain complex assembly, fatty acid beta oxidation using acyl-CoA dehydrogenase, mitochondrial ATP synthesis coupled proton transport, NADH dehydrogenase complex, proton-transporting ATP synthase complex, respiratory chain, inner mitochondrial membrane protein complex, oxidoreductase activity acting on NADPH quinone or similar compound as the acceptor, acyl-CoA dehydrogenase activity, NAD-ADP ribosyl transferase activity, and oxidoreductase activity acting on NADPH. (a) GSEA (KEGG). (b) GSEA (KEGG). (c) GSEA (biological process). (d) GSEA (cellular component). (e) GSEA (molecular function).

this part of the tissue. This phenomenon is called ischemia/reperfusion injury [17].

Spp1, known as osteopontin, is an extracellular matrix protein [18]. There are few previous studies on the relationship between Spp1 and IRI. A recent study has shown that inhibition of Spp1 expression can inhibit cell proliferation, which is a potential target for cancer therapy. Besides, scientists indicated that the postnatal inhibition of Spp1 can reduce fibrosis and facilitate motor function in DMD (Duchenne muscular dystrophy) mice through

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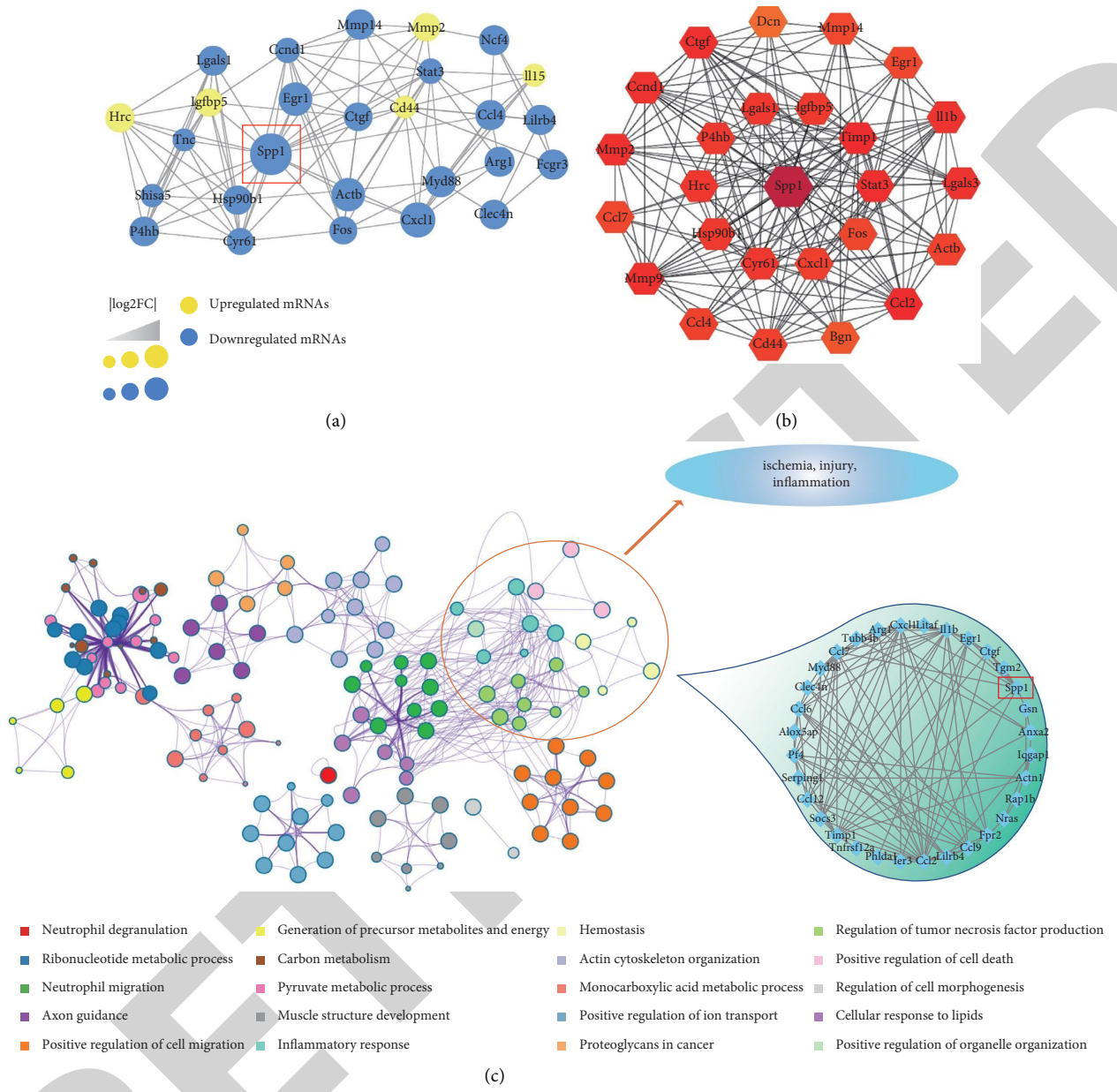

Figure 3: Spp1 was identified as the hub gene associated with ischemia, cell injury, and inflammation. (a) The PPI network indicated the interaction of 27 hub genes. (b) Hub gene network was obtained through Cytoscape, and Spp1 obtained a high score. (c) The functional clustering indicated Spp1 as a hub gene involved in ischemia, cell injury, and inflammation in the connection tissue using the Metascape database.

promoting TGF-β [19]. Also, the decrease of Spp1 expression induced by ischemia can damage neovascularization, while the overexpression of Spp1 can increase angiogenesis [20]. Furthermore, as a key mediator of neovascularization after ischemia, Spp1 would be a new target for inducing angiogenesis. The ability to form new collateral circulation is closely related to reducing long-term cardiac mortality in patients with AMI and stable CAD [21]. These studies provide clues for us to explore the relationship between Spp1 and IRI.

In this study, we downloaded the GSE83472 database for differential analysis. Afterwards, 539 RNAs were identified as DE-RNAs and used to construct the PPI network through the STRING database. A network of 400 nodes and 2085 edges was obtained for further study. According to the GO/KEEG analyses and GSEA, it was indicated that these proteins were mostly located in the cytoplasm and involved in the negative regulation of the apoptotic process and transportation. Furthermore, we identified 26 hub genes by the MCODE application of Cytoscape where the Spp1 gene achieved a high score. Besides, the hub gene network and functional clustering suggested a strong connection between Spp1 and IRI. In the end, we verified our finding in the clinical samples. Both western blotting and qRT-PCR

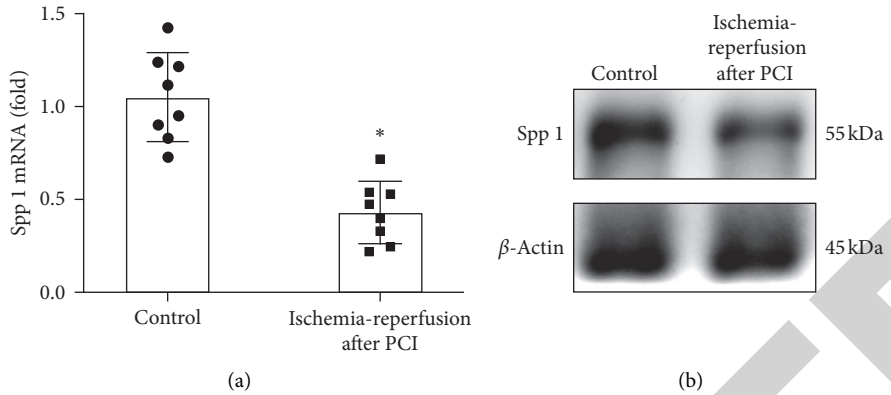

Figure 4: Downregulation of Spp1 expression in ischemia/reperfusion after PCI. (a) qRT-PCR analysis showing the expression of Spp1 in ischemia-reperfusion samples after PCI (square shape) compared to normal samples (circle shape). $^{*}p < 0.05$. (b) Western blot indicating that Spp1 protein levels were significantly downregulated in ischemia-reperfusion cells after PCI compared with normal cells.

analyses revealed the downregulation of Spp1 in acute myocardial infarction samples after IRI which may suggest the negative correlation between Spp1 and IRI. Overall, we considered that Spp1 might be regarded as a potential diagnostic biomarker in IRI because of the availability in serum and it can avoid several invasive tests.

There remain several limitations to our study such as the possible bias when analyzing DE-RNAs due to the small size of the dataset. Similarly, more blood samples from different centers can help us get more accurate results of *in vitro* experiments. Another limitation is the animal model; we did not establish a suitable animal model to validate the Spp1 level *in vivo*. Also, the related signaling pathway was needed to detect for revealing the molecular mechanism. In brief, the study on the regulation and potential pathway of genes is not complicated enough. If conditions permit, we will focus on the regulation of downstream target genes and the potential signaling pathway of Spp1.

5. Conclusions

Our study aimed to clarify the association of Spp1 with IRI through the bioinformatics analysis of the GEO database, GO/KEEG analyses, and GSEA. Furthermore, we figured out that the expression of Spp1 was downregulated in *in vitro* experiments by qRT-PCR and western blotting analyses. In the rat model of myocardial IRI, bioinformatics and integration of gene expression profiles indicated Spp1 as a hub gene closely associated with myocardial IRI, supporting the potential role in myocardial IRI.

Data Availability

All the datasets used to support the findings of this study are available from the corresponding authors upon request.

Disclosure

Ling Li and Jungang Huang are the co-first authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Ling Li and Jungang Huang contributed equally to this work.

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Retraction

Retracted: Verifying the Usefulness of Pulmonary Blood Flow Studies in the Correction of Pulmonary Atresia and Ventricular Septal Defect with Major Aortopulmonary Collateral Arteries

Cardiology Research and Practice

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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Research Article

Verifying the Usefulness of Pulmonary Blood Flow Studies in the Correction of Pulmonary Atresia and Ventricular Septal Defect with Major Aortopulmonary Collateral Arteries

Zirou Huang, Fan Cao, Rongjun Zou, Minghui Zou, Weidan Chen, Wenlei Li, Guodong Huang, Li Ma, and Xinxin Chen

Heart Center, Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, China

Correspondence should be addressed to Xinxin Chen; xinxinchengz@163.com

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Objective. We retrospectively analyzed the surgical results of pulmonary blood flow studies to guide ventricular septal defect (VSD) closure in the correction of pulmonary atresia and ventricular septal defect with major aortopulmonary collateral arteries (PA/VSD/MAPCAs). *Methods*. A total of 57 children who were diagnosed with PA/VSD/MAPCAs and who underwent intraoperative pulmonary blood flow studies at our hospital between August 2016 and June 2019 were included. Surgery and cardiopulmonary bypass records were collected. The receiver operating characteristic (ROC) curve was used to verify the accuracy of pulmonary blood flow studies to predict VSD closure. *Results*. Complete VSD closure was achieved in 39 of 57 children (68.42%), with a median age of 2 years and 5 months (range: 7 months to 15 years and 9 months) and a median weight of 11.0 kg (5.7–36.5 kg). Partial VSD repair was recorded for 21 children (36.84%), including 4 children (19.05%) who underwent VSD closure in the later stages and 13 children (61.90%) who were under follow-up and waiting to undergo complete VSD closure. There was only one child (1.75%) with VSD left. After eliminating the data of four unqualified cases, the ROC curve for predicting VSD closure based on 53 pulmonary blood flow studies was obtained at a p value of <0.001, with an area under the curve of 0.922. The maximum Youden's index was 0.713, which corresponded to an optimal mean pulmonary artery pressure cutoff value of 24.5 mmHg. *Conclusion*. The functional evaluation provided by pulmonary blood flow studies is highly accurate to predict intraoperative VSD repair. We recommend using pulmonary blood flow studies with a mean pulmonary artery pressure of ≤25 mmHg during blood perfusion at 3.0 L/min/m^2 as the standard to repair VSD.

1. Introduction

The surgical correction of pulmonary atresia and ventricular septal defect with major aortopulmonary collateral arteries (PA/VSD/MAPCAs), owing to great anatomical variations in aortopulmonary collateral arteries, remains a huge challenge. Treatment strategies can be roughly divided into two major categories. The first strategy is to perform one-stage unifocalization of pulmonary arteries as early as possible [1–3], so that the pulmonary blood supply is concentrated at the central pulmonary artery, while the associated VSD is repaired during the same stage or at a different stage. The second strategy is to promote pulmonary artery development [4]; that is, the development of native pulmonary arteries is promoted through systemic-to-pulmonary artery shunting or right ventricle to pulmonary artery connection before surgical correction of PA/VSD/MAPCAs. However, the difficulty in determining whether this condition can be corrected occurs when we evaluate pulmonary vascular bed development before VSD closure. In 1997, Reddy [1] first reported the use of pulmonary blood flow studies to evaluate pulmonary vascular development. Currently, the application of flow studies in China is still scarce, and studies using this approach have not yet been reported. Our center introduced pulmonary blood flow studies in August 2016 and adopted Reddy's standard (mean

pulmonary artery pressure ((mPAP) ≤25 mmHg) to guide VSD closure. Considering the differences in flow study methods used by different centers, it is imperative to verify the accuracy of the method used at our hospital. Therefore, we retrospectively analyzed the surgical results of pulmonary blood flow studies to guide VSD closure in children with PA/VSD/MAPCAs at our hospital.

2. Materials and Methods

2.1. Study Subjects and General Data. From August 2016 to June 2019, pulmonary blood flow studies were performed in 57 children with PA/VSD/MAPCAs during surgical correction of PA. There were 30 male (52.6%) and 27 female (47.4%) subjects. The median age of subjects who underwent flow studies was 37 months (range: 115 days to 16 years and 4 months), and the median body weight of subjects was 11.0 kg (3.8–38.0 kg). This study was approved by the Ethics Committee of Guangzhou Women and Children's Medical Center (approved no. of the ethic committee: ChiCTR-EOC-17013273), and guardians did provide informed consent.

2.2. Pulmonary Blood Flow Study Method and VSD Repair Strategy. Following unifocalization of pulmonary blood vessels, the reconstructed pulmonary artery was anastomosed with the distal end of a prosthetic conduit (autologous pericardial conduit, valved bovine jugular vein, or valved GORE-TEX vessel). Then, a pulmonary artery perfusion catheter was placed at the proximal end of the prosthetic conduit. After exhausting, the proximal end of the conduit was tightened with 10# silk thread to seal the pulmonary artery. Blood flow was supplied to the perfusion catheter using a roller pump for cardiopulmonary bypass (CPB), and the other end of the roller pump was connected to the pipeline between the CPB venous blood storage tank and major pump through a trigeminal joint. A piezometer tube was placed into the pulmonary artery prosthetic conduit to measure mPAP. The pulmonary artery was strictly exhausted, and the piezometer tube was zero-point calibrated. Meanwhile, the ascending aorta was blocked (usually at a rectal temperature of 28°C), and histidine-tryptophan-ketoglutarate solution (Dr. Franz Koehler Chemie GmbH, Bensheim, Germany) was perfused. Following cardiac arrest, the right atrium was incised, and two thick left atrial drainage tubes were placed through atrial septal incision. The roller pump of the CPB machine provided suction to the drainage tubes for sufficient drainage. Following airbag-type positive pressure ventilation to prevent atelectasis, the respiratory parameters of the anesthesia machine were adjusted to the level before CPB for normal ventilation to suck the left and right hemothorax. Pulmonary artery perfusion flow started from 0.5 L/min/m^2 and was gradually increased at a gradient of 0.5 L/min/m^2 up to 3 L/min/m^2. When the mPAP leveled off, the value was recorded. The pulmonary blood flow study was stopped if mPAP was >30 mmHg or when perfusion flow reached 3 L/min/m^2. When mPAP was ≤25 mmHg, concurrent VSD closure was anticipated; when mPAP was >25 mmHg, the VSD patch was fenestrated. Right ventricular systolic pressure (RVSP) was replaced by pulmonary artery systolic pressure, and left ventricular systolic pressure (LVSP) was replaced by peripheral systemic systolic pressure. Then, the RVSP/LVSP ratio was calculated after CPB was stopped. If the RVSP/LVSP ratio was ≤0.75, it was considered tolerable; if the RVSP/LVSP ratio was >0.75 and high-dose vasoactive drug support was required or it was difficult to maintain stable hemodynamics, ventricular septal fenestration, fenestration enlargement, or ventricular septal patch removal was performed. The size of fenestration is set in 5 mm diameter firstly as usual, with this size, and the pulmonary vascular bed should have an appropriate pressure to develop properly for further closure of VSD. If the mPAP is over 30 mmHg after fenestration, we would enlarge the fenestration until the mPAP reduces below 30 mmHg.

2.3. Statistical Analysis. All statistical analyses were performed using IBM SPSS statistics v24.0 (IBM Corp., Armonk, NY, USA). All continuous variables are expressed as mean ± standard deviation or median (range), while categorical variables are expressed as frequency and percentage. The area under the receiver operating characteristic (ROC) curve (AUC) was used to verify the accuracy of pulmonary blood flow studies to predict VSD closure.

3. Results

3.1. VSD Repair Results. In total, complete VSD closure was achieved in 39 of 57 subjects (68.42%; Figure 1). The median age of subjects was 2 years and 5 months (range: 7 months to 15 years and 9 months), and the median weight of subjects was 11.0 kg (5.7–36.5 kg). Among the procedures, 19 (48.7%) were completed in the first stage of surgery and 4 (10.2%) were completed at different stages after partial VSD repair.

There were 21 subjects (36.8%) with partial VSD repair. Among them, 19 subjects (90.5%) achieved partial VSD repair at the same stage as the flow study, 4 subjects (19.05%) underwent VSD closure in the later stages, 4 subjects (19.05%) died (see Table 1 for information on deaths), 13 subjects (61.90%) were still undergoing follow-up and were waiting for complete VSD closure, and 8 subjects (38.10%) underwent ventricular septal fenestration due to an RVSP/LVSP ratio of >0.75 and difficulty in maintaining the circulation after stopping CPB for VSD repair.

There was only one subject (1.75%) with VSD intentionally left open. The subject underwent pulmonary artery unifocalization and right ventricular to pulmonary artery connection at stage one, followed by prosthetic conduit replacement and pulmonary blood flow studies at stage two. The mPAP was 41 mmHg with a perfusion flow of 2.5 L/min/m^2, so the case with VSD intentionally left open was adopted.

3.2. Pulmonary Blood Flow Study Results. Among the 57 children who underwent pulmonary blood flow studies, three failed to reach full perfusion flow (mPAP was 25, 41, and 38 mmHg, respectively, at 2.5 L/min/m^2). In another

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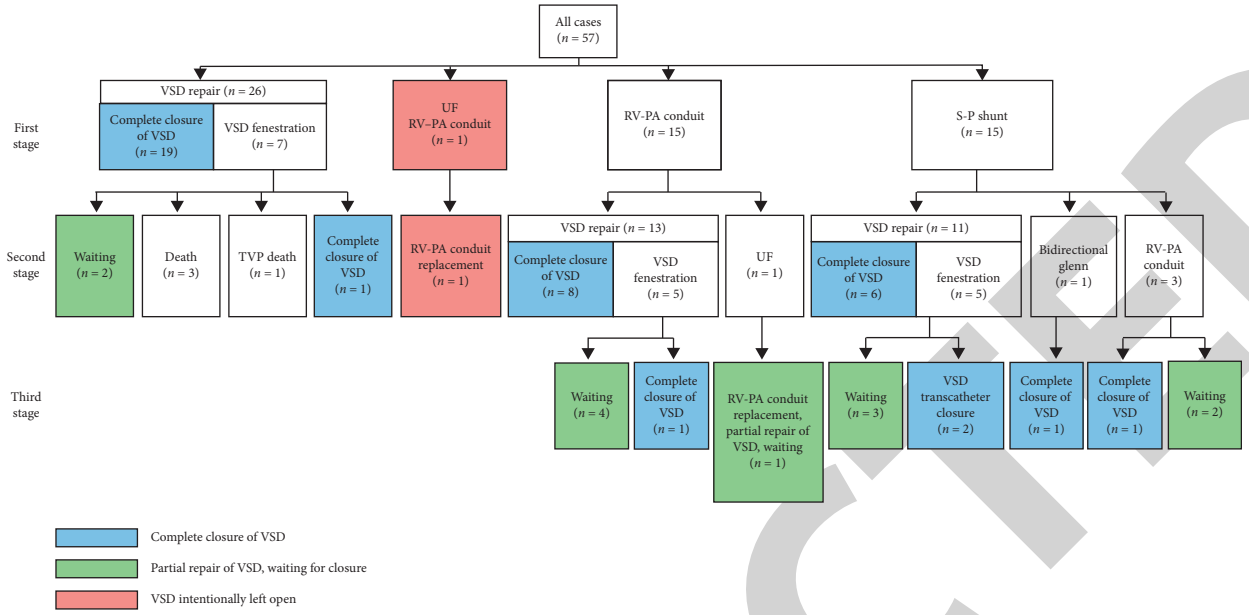

Figure 1: Surgical process for the whole group of subjects with PA/VSD/MAPCAs (RV-PA: right ventricle-pulmonary artery; TVP: tricuspid valvuloplasty; UF: pulmonary artery unifocalization; VSD: ventricular septal defect).

Table 1: Cause of death.

No.	Age (month)	Weight (kg)	Classification	Operation histories	Treatment	VSD status	Salvage VSD fenestration	mPAP (mmHg)	RVSP/LVSP	Interval after treatment	Cause of death
1	81	22.6	III	RV-PA conduit Unifocalization Partial repair of VSD	Conduit replacement Tricuspid valvuloplasty	Partial repair of VSD	No	32	0.9	10 days	Intracranial infection
2	16	8.5	IV		RV-PA conduit Unifocalization Partial repair of VSD	Partial repair of VSD	Yes	20	1.14	3 months	Sudden cardiac death (outside hospital)
3	55	14.4	IV		RV-PA conduit Unifocalization Partial repair of VSD	Partial repair of VSD	Yes	30	1.1	1 day	Hypoxia, low cardiac output syndrome
4	6	5	III		RV-PA conduit Partial repair of VSD	Partial repair of VSD	Yes	38 (when 2.5 L)	1.14	22 days	Cardiac failure

case, mPAP was 8 mmHg, and after complete VSD repair, the RVSP/LVSP ratio was 1.16, so treatment was changed to rescue ventricular septal fenestration. Considering that left pulmonary artery hemorrhage during the flow study could affect the results, these four children were eliminated.

A scatter plot of mPAP and RVSP/LVSP ratio for the remaining 53 subjects is shown in Figure 2. The mean mPAP was 21.02 ± 6.12 mmHg (10–32 mmHg), and the mean RVSP/LVSP ratio was 0.73 ± 0.20 (0.4–1.14). At the same stage as flow study, there was one subject with VSD intentionally left open (mPAP was 32 mmHg, and RVSP/LVSP ratio was 0.9), 36 subjects with complete VSD repair (mPAP was 17.94 ± 5.14 mmHg, and RVSP/LVSP was 0.71 ± 0.16), and 16 subjects with partial VSD repair (mPAP was 26.88 ± 4.21 mmHg, and RVSP/LVSP was 0.88 ± 0.17). At the same stage as the pulmonary blood flow study, one case with an mPAP of >25 mmHg completed VSD repair, whereas six cases with an mPAP of ≤25 mmHg underwent partial VSD repair and hole fenestration. The ROC curve of the pulmonary blood flow study for predicting VSD closure

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is shown in Figure 3, with an AUC of 0.922, 95% CI of 0.845–1.000 and maximum Youden's index of 0.713 ($p < 0.001$).

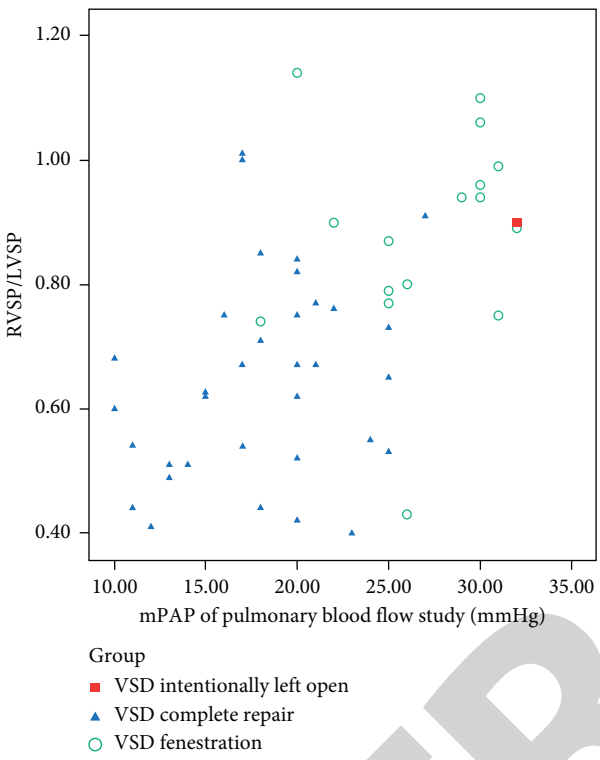

Figure 2: Scatter plot of mPAP (mean pulmonary artery pressure) and postoperative RVSP (right ventricular systolic pressure)/LVSP (left ventricular systolic pressure) ratio for 53 subjects who underwent pulmonary blood flow studies.

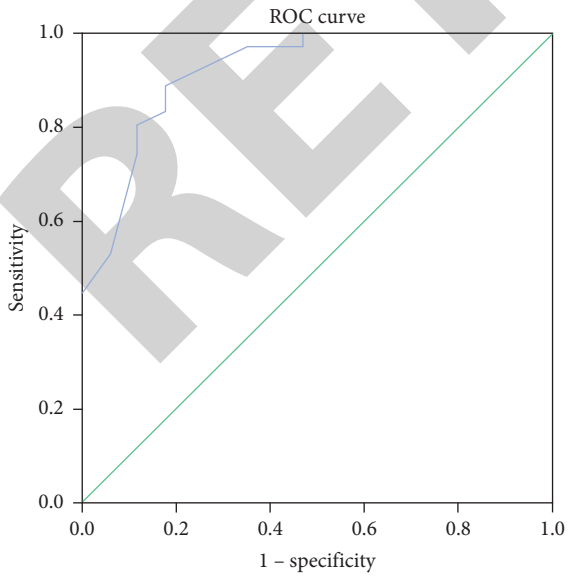

Figure 3: The ROC curve of mPAP (mean pulmonary artery pressure) measured by pulmonary blood flow studies to predict VSD closure ($p < 0.001$; area under the curve = 0.922, 95% confidence interval 0.845–1.000, maximum Youden's index = 0.713).

4. Discussion

Traditional evaluation standards for pulmonary artery development in patients with PA/VSD include the Nakata index and McGoon ratio [5]. Because children with type C PA/VSD have MAPCAs, pulmonary vascular indices alone cannot fully reflect the state of the entire pulmonary vascular bed. Therefore, Reddy et al. [1] proposed the concept of total neopulmonary artery index (TNPAI), which lists pulmonary arteries, together with MAPCAs planned to be unifocalized and included into the pulmonary circulation, in the calculation formula. Therefore, TNPAI is relatively comprehensive in evaluating pulmonary vascular development among patients with type C PA/VSD, and it can be used as one of the important indices for preoperative pulmonary vascular evaluation. In cases with a TNPAI of >150 mm^2/m^2, there is a greater chance of concurrent VSD closure. However, TNPAI also has some limitations [6]. First, TNPAI is an index calculated based on image data with certain errors. Second, when MAPCAs are narrowed or distorted, use of TNPAI is controversial. Third, unifocalized MAPCAs included into the pulmonary circulation may be distorted, angular, stenosed, or even blocked due to surgery. Consequently, there will be differences between the actual surgical effect and the result predicted by preoperative estimation of TNPAI.

Considering the limitations of morphological evaluation, in 1997, Reddy proposed intraoperative pulmonary hemodynamic studies to evaluate development of the pulmonary circulation, namely, pulmonary blood flow studies. The initial approach was to place an arterial cannula and a pulmonary artery piezometer tube into the reconstructed central pulmonary artery following unifocalization of pulmonary blood vessels, followed by blood flow perfusion at 2.5 L/min/m^2 using a roller pump of a CPB machine with simultaneous mPAP measurement. The principle is to simulate pulmonary artery perfusion with a physiological pulmonary blood flow. If mPAP is higher than the preset cutoff value, the pulmonary vascular bed is underdeveloped and is thus not sufficient to withstand the entire blood flow ejected from the right ventricle, which prevents complete VSD repair.

The practice of pulmonary artery perfusion studies varies across different centers. Matteo's team [7] chose to completely collapse both the lungs under the condition of a beating heart and then perfuse the pulmonary arteries with oxygenated blood. In contrast, Honjo [8] performed a flow study with both the lungs ventilated normally after cardiac arrest. In the CPB state, many factors can affect mPAP results [7, 8]. On the one hand, blood dilution and oxygenated blood perfusion reduce pulmonary circulatory resistance, leading to a decrease in mPAP; on the other hand, pulseless perfusion, hypothermia, inadequate left atrial drainage, pulmonary collapse, and positive pressure ventilation enhance blood flow resistance, leading to an increase in mPAP. Other factors, such as imprecise suturing of pulmonary artery prosthetic conduit, can also affect the results of flow studies. In this article, one subject bled from the left pulmonary artery anastomosis and prosthetic

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conduit, which led to a very low mPAP in the upcoming pulmonary blood flow study (mPAP = 8 mmHg). Following complete VSD repair, the RVSP/LVSP ratio was 1.16 and hemodynamics could not be maintained, so the case was changed to rescue ventricular septal fenestration.

Under the influence of many factors, the same subject may not produce identical results using different flow study methods, so the standards adopted by different centers are also variable. The standard adopted by multiple centers is an mPAP of ≤30 mmHg with a pulmonary artery blood flow perfusion rate of 2.5 L/min/m^2. In recent studies, Reddy's team changed the standard to a perfusion flow of 3.0 L/min/m^2 and an mPAP of ≤25 mmHg, which predicts that the VSD can be completely closed [9, 10]. This standard has always been used by our center. Here, the ROC curve of pulmonary blood flow studies was obtained at p value of <0.001 (AUC = 0.922), indicating a high accuracy in predicting VSD closure. The maximum value of Youden's index was 0.713, and the corresponding cutoff value for mPAP was 24.5 mmHg, which is highly consistent with the mPAP standard of ≤25 mmHg used at our center.

VSD repair guided by flow studies failed in seven cases (13.2%) in the present study. There was one case with an mPAP of >25 mmHg (27 mmHg); however, considering that a catheter examination revealed good pulmonary vascular bed development, and combined with a slightly elevated mPAP, this case underwent complete VSD repair. The child had a postoperative RVSP/LVSP ratio of 0.91, and the circulation was well tolerated. Additionally, there were three cases with an mPAP of <25 mmHg in whom intraoperative perforation of the ventricular septal patch was performed. In these patients, mPAP was 18, 20, and 22 mmHg, respectively, and the concurrent postoperative RVSP/LVSP ratio was 0.74, 1.14, and 0.90, respectively. Furthermore, there were three cases with an mPAP of 25 mmHg in whom the postoperative RVSP/LVSP ratio was 0.77, 0.79, and 0.87, respectively. The failure rate of pulmonary blood flow studies to guide VSD closure was approximately 6.32%–15% in previous studies. Overall, the method and standard of pulmonary flow studies used at our center are relatively accurate to guide VSD closure, although some factors affect the accuracy of this approach.

A total of four children died in the present study, and all deaths occurred after one-stage flow studies with partial VSD repair. Only one case with an mPAP of <25 mmHg died suddenly out of hospital due to an unknown cause. The remaining three children who died in hospital had an mPAP of ≥30 mmHg; one died due to noncardiogenic intracranial infection, one due to sudden death, and one due to heart failure. The latter two cases were treated with preoperative rescue ventricular septal fenestration and enlargement. There were no deaths in children who underwent complete VSD repair or staged partial VSD repair. Zhu [10] found that VSD closure is a high risk in children with an mPAP of ≥25 mmHg, for whom a careful evaluation is needed and in whom the indications for ventricular septal fenestration should be extended. In contrast, patients with an mPAP of <25 mmHg have a very high midterm survival rate, regardless of the anatomical conditions of pulmonary arteries and MAPCAs.

Matteo [7] retrospectively analyzed 95 patients with PA/VSD/MAPCAs who underwent pulmonary blood flow studies after completing pulmonary vascular unifocalization. An inability to complete exact intracardiac repair was a predictor of mortality, whereas the long-term outcomes of patients with complete VSD repair were satisfactory. Matteo contended that children with a low mPAP have a well-developed vascular bed and stable postoperative hemodynamics; however, the mPAP threshold above which the survival rate of children is affected still needs to be explored. Meanwhile, Matteo found no difference in the survival rates of those who achieved complete VSD repair in one stage compared with those who achieved complete VSD repair in multiple stages. This conclusion was also corroborated by Stanford's team [11]. Multiple studies have suggested that cases with an unsatisfactory mPAP and morphological results should be treated with caution using conservative strategies. In our study, the subjects who died in hospital had high mPAP values, underdeveloped pulmonary vascular beds, and high postoperative RVSP/LVSP ratios. For such patients, pulmonary vascular development should be carefully evaluated based on preoperative morphological data to prevent the risk of increased right heart load caused by earlier VSD repair.

This study has certain limitations. First, due to the limitations of retrospective data, factors affecting the accuracy of flow studies in predicting VSD closure were not identified. Second, the sample size of the study was relatively small; thus, the results need to be further verified in large-sample studies.

5. Conclusions

This study retrospectively analyzed the application of pulmonary blood flow studies in children with PA/VSD/MAPCAs at our hospital. Pulmonary blood flow studies are highly accurate to predict intraoperative repair of VSD through functional evaluation. We recommend an mPAP of ≤25 mmHg during pulmonary artery perfusion with a blood flow of 3.0 L/min/m^2 under the condition of normal ventilation with a ventilator and sufficient drainage of the left heart after cardiac arrest for VSD repair.

Data Availability

All of the data and analysis results are available from the corresponding author upon request.

Conflicts of Interest

The authors state that they have no conflicts of interest.

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Research Article

Patients with New-Onset Tumor of Severe Coronary Artery Disease May be at a Higher Risk of Arrhythmia

Palisha Alimu,[1] **Dezhi Yang**,[2] **Huatao Zhou**,[3] **Yan Wu**,[4] **and Huiping Guo**[3]

[1]*Department of Emergency Medicine, Sun Yat-sen Memorial Hospital, Sun Yat-set University, Guangzhou, China*
[2]*Department of Cardiovascular Medicine, The People's Hospital of HeChi, Hechi, China*
[3]*Department of Cardiovascular Medicine, Sun Yat-sen Memorial Hospital, Sun Yat-set University, Guangzhou, China*
[4]*Department of Oncology Medicine, The People's Hospital of HeChi, Hechi, China*

Correspondence should be addressed to Huatao Zhou; 13631334763@163.com

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Background. Arrhythmia is one of the causes of death in severe coronary artery disease patients who also suffered from cancer. Our research aims to compare the incidence of arrhythmia between severe coronary artery disease patient with and without new-onset tumor. *Methodology*. We enrolled 79 patients (December 2019–December 2020) with severe coronary artery disease in this study, and 40 of them were complicated with new-onset tumor. The details of all subjects were thoroughly obtained; the laboratory tests were implemented including creatinine before coronary angiography. The appraisal of the severity of coronary artery disease was applied by Gensini score. The cardiac inspection includes UCG, 12-lead ECG, and Holter monitor. *Results*. Among them, there were 40 patients in the experimental group and 39 patients in the control group. The difference at the baseline between the two sets of figures was not statistically significant ($P > 0.05$). The incidence of arrhythmia between the two groups was statistically significant ($P < 0.05$). *Conclusions*. The incidence of arrhythmia in severe coronary artery disease patients who were complicated with new-onset tumor was higher than that in patients with severe coronary artery disease alone, and attention should be paid to arrhythmia before tumor treatment.

1. Introduction

Although mortality rates of coronary heart disease and tumors have declined, they remain the leading causes of death in humans [1, 2]. Arrhythmia is very common in patients with coronary heart disease complicated with tumor [3]. Cognition and management of arrhythmia require an understanding of common etiologies and incidence [4]. Mechanisms of arrhythmia in cancer patients include direct cardiac involvement by cancer or cancer treatment-induced arrhythmia including radiation, chemotherapy, and surgery [5]. Coronary artery disease is also one of the risk factors for arrhythmia, and previous studies have shown that the heavier coronary lesions had higher incidence of arrhythmia and, at the same time, the worse prognosis [6]. Gensini scores are often used in clinical trials to assess coronary artery severity [7]. Few studies had been conducted on arrhythmia in cancer patients complicated by severe coronary artery disease. Improper recognition or treatment of arrhythmia may lead to adverse clinical consequences. Clinically, little attention has been paid to arrhythmia before tumor treatment. The study was aimed at comparing the difference of the two groups in the incidence of arrhythmia.

2. Patients and Methods

We conducted a controlled cross-sectional retrospective analysis. A total of 40 patients with new-onset tumor diagnosed in our hospital and coronary angiography suggesting severe coronary artery disease at the same time in hospital from December 2019 to December 2020 were selected, and 39 nontumor patients diagnosed with severe

Table 1: Baseline demographic characteristics.

Characteristics	Severe coronary artery lesions combined with new-onset tumor ($n = 40$)	Severe coronary artery lesion group ($n = 39$)	P value
Age	70.83 ± 9.14	68.90 ± 11.97	0.423
Gender, male (n)	33 (82.5%)	28 (71.8%)	0.257
Hypertension (n)	28 (70%)	30 (76.99%)	0.486
Diabetes (n)	15 (37.5%)	13 (33.3%)	0.699
Smoking (n)	17 (42.5%)	15 (38.5%)	0.715
Creatinine (μmol/L)	124.95 ± 162.93	99.38 ± 91.99	0.395
hs-CRP	14.28 ± 28.85	8.57 ± 16.94	0.282
LVEF (%)	62.03 ± 9.15	63.13 ± 10.39	0.618
LA (mm)	36.80 ± 4.60	36.33 ± 6.27	0.707
Gensini score	54.94 ± 26.42	55.78 ± 34.90	0.905

Table 2: Comparison of prevalence in arrhythmia between two groups.

	Severe coronary artery lesions combined with new-onset tumor ($n = 40$)	Severe coronary artery lesion group ($n = 39$)	Chi square (χ^2) test
Prevalence of arrhythmia (n)	24 (60%)	10 (25.6%)	$P = 0.002$

coronary artery disease undergoing coronary angiography during the same period were randomly selected. Exclusion criteria included serious lung disease, thyroid dysfunction, acute infection, rheumatism, immune diseases, and chronic inflammatory disease. In this study, all enrolled patients underwent clinical evaluation and laboratory screening, and informed consent was obtained from all patients. Past medical history and clinical data, including age, gender, hypertension, diabetes, creatinine level, and cardiac function were all collected. The condition and severity of coronary artery lesions were evaluated by coronary angiography. The stenosis degree of all lesions was completed through at least two sections, and the Gensini score was calculated. The arrhythmia was mainly evaluated using 12-lead ECG and Holter monitor. SPSS 26 software was used for data analysis. Using Student's t-test numerical variables were compared between the study groups for independent samples. Chi square (χ^2) test was carried out for comparing categorical data. P values less than 0.05 were regarded as statistically significant.

3. Results

A sum of 79 patients enrolled in the study comprising the severe coronary artery lesion group of 39 people and severe coronary lesions combined with new-onset tumor group of 40 people. There was no statistical significance between the two groups in relation to age, gender, hypertension, diabetes, LVEF, Gensini scores, and so on ($P > 0.05$) which is shown in Table 1. We observed in our study that the incidence of arrhythmia in the severe coronary artery disease group with new-onset tumor was 60% and another group was 25.6%. This difference between the two groups was statistically significant ($P < 0.05$), which is shown in Table 2. Attention should be paid to arrhythmia before the tumor is treated.

4. Discussion

In our study of severe coronary artery disease patients with new-onset tumor, the final results show a higher incidence of cardiac arrhythmia than the patients without tumor complication. Although the association of cardiac arrhythmia with coronary artery disease (CAD) or cancer has long been paid attention to, there still exists little research regarding the relation between the severity of CAD and the prevalence of cardiac arrhythmia in new-onset cancer patients. The etiology of arrhythmias in cancer patients has not been clear yet, despite the anticancer therapy factor, which may be a result of the direct cardiac involvement of the primary cancer or metastasis to heart [8, 9]. Cancer itself is able to lead to arrhythmia, especially atrial fibrillation/flutter (AF/AFL) and ventricular arrhythmia. There is some hypothesis to explain the mechanisms of arrhythmias in cancer patients on the cellular level, including abnormal calcium homeostasis, mitochondrial injury, and cardiac apoptosis [10–12].

In this study, as previously mentioned, arrhythmia, especially atrial fibrillation and ventricular premature beats, was linked to a new-onset cancer group with a higher number of diseased coronary vessels. Repetitive arrhythmia occurred in 60 percent of multivessel CAD patients with new-onset cancer compared with 25.6 percent of those without cancer. The incidence of AF and premature beats was also nearly twofold in the former

group. AF is regarded as a highly prevalent complication among patients with cancer history [13]. In addition, a previous study shows a remarkably higher prevalence of multivessel disease in patients with atrial fibrillation [9]. This is in accordance with the findings of ours. This observation is consistent with previous studies, which explored the extent of CAD in patients with AF [14–16]. Since patients with severe coronary artery disease are prone to have poor left ventricular pump function, cancer may somehow accelerate the process of heart failure. [14, 17]. This susceptibility may be related to gathering of cardiovascular risk factors in cancer patients and possibly a shared physiopathology that leads to both malignancy and CAD development in new-onset oncological patients who have not experienced the antineoplastic therapy. All of these mentioned cardiac pathologies are known to drive the incidence of AF [17, 18]. So, severe cardiac functional insufficiency seems more likely to be a trigger for atrial fibrillation in this group as well [14].

Our study revealed no significant difference in the incidence of ventricular arrhythmia between two groups. Previous study shows that ventricular fibrillation is related to a larger amount of ischemic myocardium caused by occlusion of major coronary arteries and lower remnant blood flow in myocardial infarction [19, 20]. Furthermore, it has been shown that patients with malignant arrhythmias had greater numbers of diseased coronary arteries than those who demonstrated infrequent or no ectopic activity [21, 22]. When the myocardium is invaded by tumor, irritation of the heart conduction system can lead to ventricular and supraventricular ectopy [8]. However, there were few studies which have drawn attention to the association between cancer-related ventricular arrhythmia and the extent of coronary vascular involvement.

Severe coronary artery disease patients with cancer might have a higher risk for being amalgamated with cardiac arrhythmias, and attributing this finding to mere coincidence appears inconsequent. The molecular mechanism of cancer-induced cardiac electrophysiology disorder has not been clear yet [23]. Moreover, neurohormonal activation might stimulate atrial or ventricular arrhythmias in CAD with cancer because it has already been shown in previous studies [23, 24]. Larger sample sizes are needed to confirm the effect of cancer on the cardiac arrhythmia in severe CAD patients.

5. Conclusion

In our study, patients with severe coronary artery disease complicated with new-onset tumor had higher a incidence of arrhythmia than in patients with severe coronary artery disease alone. Tumor may be a health hazard of cardiac arrhythmia in those patients, and morden medicine should pay more attention to it before cancer treatment.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

Palisha Alimu and Dezhi Yang are the first and second authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Palisha Alimu and Dezhi Yang contributed equally to this study.

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Retraction

Retracted: High-Density Lipoprotein Cholesterol in Young Nondiabetic Coronary Heart Disease Patients

Cardiology Research and Practice

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] Z. Hu, J. Cui, X. Li, Y. Zhou, L. Cai, and S. Zhang, "High-Density Lipoprotein Cholesterol in Young Nondiabetic Coronary Heart Disease Patients," *Cardiology Research and Practice*, vol. 2021, Article ID 2970568, 5 pages, 2021.

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Research Article

High-Density Lipoprotein Cholesterol in Young Nondiabetic Coronary Heart Disease Patients

Ziyang Hu,[1] **Jingle Cui**,[2] **Xueshan Li**,[1] **Yaohui Zhou**,[3] **Lu Cai**,[4] **and Shibin Zhang**[5]

[1]*Department of Cardiology, Zhongshan Hospital of Traditional Chinese Medicine, Zhongshan 528400, China*
[2]*Department of Cardiothoracic Surgery, Zhongshan Hospital of Traditional Chinese Medicine, Zhongshan 528400, China*
[3]*Emergency Department, Zhongshan Hospital of Traditional Chinese Medicine, Zhongshan 528400, China*
[4]*Department of Clinical Laboratory, Zhongshan Hospital of Traditional Chinese Medicine, Zhongshan 528400, China*
[5]*Graduate School of Hunan University of Chinese Medicine, Changsha 410208, China*

Correspondence should be addressed to Ziyang Hu; huziyang2007@126.com

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Objective. To investigate the association between the lipid profiles and coronary heart disease (CHD) in nondiabetic patients younger than 65 years of age. *Method*. 424 patients were enrolled in this study from January 2019 to December 2020. All the patients were screened for clinically indicated coronary angiography. They were divided into two groups according to the coronary angiography results: 340 patients with the presence of CHD (at least one coronary artery stenosis ≥50%) were classified as the CHD group, and the rest with the absence of CHD comprised the normal group. The demographic data and lipid profiles were compared. *Result*. CHD was higher in males than females (84.5% *vs*. 62.2%, $P < 0.001$). In the CHD group, the level of high-density lipoprotein cholesterol (HDL-C) was lower ($P < 0.001$), while the triglyceride (TG)/HDL-C ratio was higher ($P = 0.022$). No significant differences were shown between the two groups in terms of age, family history of CHD, hypertension, and the levels of TC, TG, and LDL-C. Gender differences were further explored. In men, except for the level of HDL-C which was significantly lower in the CHD group than that in the normal group ($P = 0.017$), parameters were comparable. A binary logistic regression model further indicated that HDL-C was associated with CHD (OR = 0.137, 95%CI: 0.031–0.594, $P = 0.008$). Also, with the increase of the number of coronary artery with lesions, the levels of HDL-C decreased significantly in men. In women, no differences were observed between the CHD group and normal group. *Conclusion*. HDL-C may be inversely associated with the risk of CHD in young nondiabetes patients, especially in men. More research is needed to confirm it.

1. Introduction

In spite of a remarkable decline in death rates from cardiovascular disease (CVD) observed over the last decades, CVD still remains the leading cause of total years of life lost globally [1, 2]. Coronary heart disease (CHD) and stroke were the most common causes of CVD deaths. The pathological basis for CHD and stroke was atherosclerosis featured by the accumulation of plaques in vessel walls [3]. Dyslipidemia is an important risk factor for CHD and stroke. A strong relationship has been established between a higher level of low-density lipoprotein cholesterol (LDL-C) or a lower level of high-density lipoprotein cholesterol (HDL-C) with an increasing risk for CHD [4]. Moreover, an increasing amount of evidence has showed that an elevated level of triglyceride (TG) is independently associated with an increased risk of CHD [4, 5]. Recently, the ratio of TG/HDL-C was found to be closely related to insulin resistance, metabolic syndrome, and diabetes [6–9]. Known as a well-defined atherogenic plasma index, the TG/HDL-C ratio was also indicated to be an important predictor for CHD [10–12] by reflecting the balance between atherogenic and protective lipoproteins [13].

Gender differences have also been reported in the prevalence, clinical presentation, and outcomes of CVD [14, 15]. Due to the higher life expectancy than men do, women form a larger proportion of the elderly population in which the prevalence of CVD is the highest. However, when

adjusted for differences in age distribution, the CVD mortality and morbidity rates are the highest in men than that in women. So far, the basic epidemiological characteristics of CHD are diseases of the middle-aged and elderly population, but there is a pronounced tendency of younger age [16]. However, studies regarding the relation between CHD and lipid profiles according to gender have been rarely reported, especially in those young adults.

Thus, in the present study, we conducted a retrospective study to investigate the association between the lipid profiles and CHD in nondiabetic patients younger than 65 years of age.

2. Methods

2.1. Patients. 424 patients admitted to the Zhongshan Hospital of Traditional Chinese Medicine from January 2019 to December 2020 were enrolled in this study. All the patients were screened for clinically indicated coronary angiography. The exclusion criteria were as follows: (1) younger than 18 or older than 65; (2) diagnosed as diabetes; (3) severe congenital heart disease; (4) severe valvular heart disease; (5) high-powered heart disease, such as hyperthyroidism and severe anemia; (6) pulmonary heart disease; (7) hypertrophic obstructive cardiomyopathy; (8) severe liver and/or renal insufficiency and malignancy; or (9) severe hematologic disorders. The patients were divided into two groups according to the coronary angiography results: 340 patients with the presence of CHD (at least one coronary artery stenosis ≥50%) were classified as the CHD group, and the rest with the absence of CHD comprised the normal group. The study protocol was approved by the institutional ethics committee of Zhongshan Hospital of Traditional Chinese Medicine, and informed consent for their clinical data to be used for research purposes was obtained from all participants.

2.2. Data Collection. The demographic data and laboratory data were obtained from case records. The demographic data included age, gender, body mass index (BMI), family history of CHD, hypertension, diabetes, and smoking. Hypertension was defined as a repeated systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg (at least 2 times in different environments) or currently taking antihypertensive drugs. Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L; 2-hour plasma glucose >11.1 mmol/L during an oral glucose tolerance test (OGTT); or active use of hypoglycemic drugs. Smoking was determined as a previous history of smoking or active smoking. The laboratory data included lipid profiles, cardiac markers, biochemical parameters, and hemogram. Some parameters were obtained during admission to the hospital. After an overnight fasting, blood samples for lipid profiles, including total cholesterol (TC), TG, HDL-C, and LDL-C, were obtained. All the blood samples were delivered into the laboratory of the hospital. The blood samples for lipid profiles were analyzed using standard methods, without any delay.

2.3. Coronary Angiography. Coronary angiography was performed using the UNIQ Clarify FD20 equipment (Philips, the Netherlands). All procedures followed the standard American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for coronary angiography. The coronary angiograms were evaluated by experienced interventional cardiologists.

2.4. Statistical Analysis. Continuous variables were presented as the mean ± standard error (SD), and categorical variables were presented as frequencies and percentages. Appropriate statistical tests were used for comparison, including the Mann–Whitney U test, chi-square test, Fisher's exact test, and one-way ANOVA. A binary logistic regression model was used to investigate the risk factors of CHD in nondiabetic patients. The presence or absence of CHD was used as a dependent variable. The variables demonstrating differences between patients with or without CHD (entry criterion $P < 0.1$) or those that had been reported to be associated with CHD were included in the regression analysis with the enter method. The statistical analysis was performed with the Statistical Package for Social Sciences (SPSS, version 16.0 for Windows). $P < 0.05$ was considered statistically significant.

3. Results

The average age of 424 patients was 53.1 ± 8.5 (years) (range: 23–65). Table 1 showed the baseline characteristics of the patients. CHD was higher in males than females (84.5% *vs.* 62.2%, $P < 0.001$). More smokers were in the CHD group than that in the normal group ($P = 0.001$). In the CHD group, the TG/HDL-C ratio was higher ($P = 0.022$), while the levels of HDL-C were lower ($P < 0.001$). No significant differences were shown between the two groups in terms of age, family history of CHD, hypertension, and the levels of TC and LDL-C.

Gender differences were further investigated. In men, except for the level of HDL-C which was significantly lower in the CHD group than that in the normal group ($P = 0.017$), parameters were comparable between these two groups (Table 2). However, in women, no significant differences were observed between the CHD group and normal group (Table 2). The binary logistic regression model indicated that, in nondiabetic men, HDL-C was associated with CHD (OR = 0.137, 95%CI: 0.031–0.594, $P = 0.008$), but showed no associations with the remaining risk factors including hypertension, smoking, family history of CHD, TC, TG, LDL-C, and TG/HDL-C.

Figure 1 presents the levels of HDL-C grouped by the number of coronary artery with lesions in nondiabetic men. The average levels of HDL-C in each group were 1.16 ± 0.42 (mmol/L, normal group, $n = 53$), 1.03 ± 0.24 (mmol/L, single-vessel group, $n = 87$), 1.02 ± 0.25 (mmol/L, two-vessel group, $n = 93$), and 0.99 ± 0.24 (mmol/L, three-vessel group, $n = 109$), respectively. A significant decrease was observed among these groups ($P = 0.044$). Further multiple comparisons showed that the level of HDL-C was

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Table 1: Characteristics of patients without diabetes in the CHD group and normal group.

	CHD group ($n = 340$)	Normal group ($n = 84$)	P value
Age (y)[a]	53.2 ± 8.2	52.8 ± 9.6	0.929
Gender[b]			<0.001*
Female	51 (62.2)	31 (37.8)	
Male	289 (84.5)	53 (15.5)	
Family history of CHD, n (%)[b]	30 (8.8)	7 (8.3)	0.887
Hypertension, n (%)[b]	182 (53.5)	38 (45.2)	0.173
Smoking, n (%)[b]	164 (48.2)	23 (27.4)	0.001*
Lipid profiles[a]			
TC (mmol/l)	5.12 ± 1.43	5.06 ± 1.16	0.842
TG (mmol/l)	1.88 ± 1.42	1.79 ± 1.42	0.261
HDL-C (mmol/l)	1.04 ± 0.26	1.21 ± 0.39	<0.001*
LDL-C (mmol/l)	3.11 ± 1.17	2.97 ± 0.89	0.418
TG/HDL-C ratio	1.99 ± 1.80	1.71 ± 1.61	0.022*

[a]Mann–Whitney U test was used for the analysis. [b]Chi-square test was used for the analysis. *A statistically significant difference ($P < 0.05$).

Table 2: Characteristics of patients without diabetes in the CHD group and normal group in different genders.

	Male gender			Female gender		
	CHD group	Normal group	P value	CHD group	Normal group	P value
n	289	53		51	31	
Age (y)[a]	52.6 ± 8.5	50.7 ± 10.1	0.314	56.5 ± 6.1	56.4 ± 7.7	0.935
Family history of CHD, n (%)	29 (10.0)	6 (11.3)	0.776[b]	1 (2.0)	1 (3.2)	1.000[c]
Hypertension, n (%)[b]	149 (51.6)	21 (39.6)	0.110	33 (64.7)	17 (54.8)	0.374
Smoking, n (%)	162 (56.1)	22 (41.5)	0.051[b]	2 (3.9)	1 (3.2)	1.000[c]
Lipid profiles[a]						
TC (mmol/l)	5.06 ± 1.42	4.84 ± 1.12	0.304	5.44 ± 1.49	5.42 ± 1.14	0.841
TG (mmol/l)	1.86 ± 1.43	1.73 ± 1.30	0.238	1.99 ± 1.33	1.88 ± 1.62	0.351
HDL-C (mmol/l)	1.01 ± 0.24	1.16 ± 0.42	0.017*	1.22 ± 0.28	1.28 ± 0.33	0.332
LDL-C (mmol/l)	3.11 ± 1.16	2.88 ± 0.88	0.199	3.08 ± 1.26	3.11 ± 0.89	0.752
TG/HDL-C	2.02 ± 1.84	1.72 ± 1.52	0.094	1.85 ± 1.56	1.68 ± 1.80	0.320

[a]Mann–Whitney U test was used for the analysis. [b]Chi-square test was used for the analysis. [c]Fisher's exact test was used for the analysis. *A statistically significant difference ($P < 0.05$).

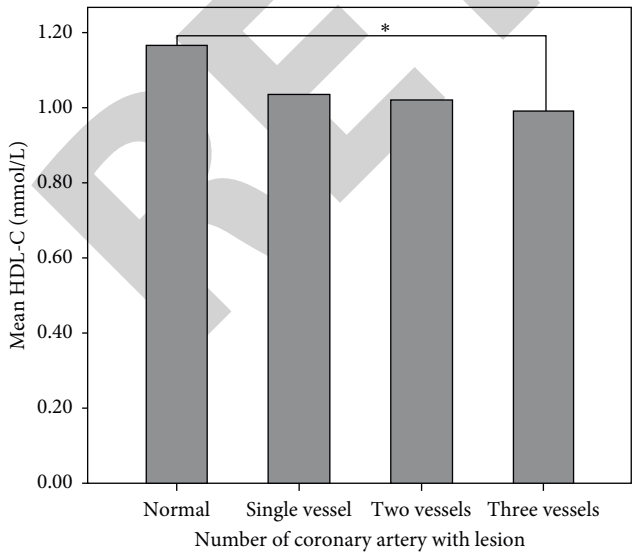

Figure 1: The levels of HDL-C in nondiabetic men grouped by different numbers of coronary artery with lesion ($P < 0.05$) (one-way ANOVA was used for the analysis, and * denotes further multiple comparisons: normal *vs*. three vessels ($P < 0.05$)).

significant lower in the three-vessel group than in the normal group ($P = 0.037$).

4. Discussion

CHD is one of the leading causes of death worldwide with a trend to be younger, despite the remarkable progress in the research of molecular and pathological mechanisms and treatment of it [17–23]. Identifying risk factors and adequate management is one of the corner stones of preventing CHD. It is meaningful to explore the risk factors of CHD in young adults. Diabetes is associated with increased CHD morbidity and mortality. Patients with diabetes are also more prone to heart failure, arrhythmias, and sudden cardiac death. Furthermore, coronary interventions performed in such high-risk patients have worse outcomes. "Atherogenic dyslipidaemia" is a characteristic of lipid profiles in type 2 diabetes mellitus [24]. Thus, in order to eliminate the interference of diabetes on results, we conducted this retrospective study in nondiabetic patients younger than 65 years of age. The results of the present study indicated that the levels of HDL-C and TG/HDL-C ratio might be associated with the risk of CHD in nondiabetic patients younger than 65 as well.

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However, the level of LDL-C between the CHD group and normal group showed no significant differences. We speculated that it might be related to the age- and gender- specific differences. It has been reported that fluctuating increasing and decreasing LDL-C levels occurred with phases of aging in both sexes [25].

HDL-C lipoproteins are the smallest (5–17 nm) and densest (1.063–1.210 kg/L) in the plasma. Many clinical and epidemiological studies have clearly demonstrated that the HDL-C is inversely correlated with the risk of CHD and is a critical and independent component of predicting this risk [26]. Our results confirmed this opinion again in young nondiabetic patients. The mechanisms that HDL-C is associated with CHD are currently unclear. HDL-C is demonstrated to play antioxidative and anti-inflammatory effects as well as improvement of endothelial function, alongside the prominent role in reverse cholesterol transport [27–29]. In addition, HDL-C can have antithrombotic and profibrinolytic effects [30]. Thus, the lower level of HDL-C might weaken these protective effects, which lead to the occurrence of atherosclerosis, the most common cause of CAD pathogenesis.

Recently, the TG/HDL-C ratio was also reported to be related to CHD. It has been demonstrated that the TG/HDL-C ratio may be an important predictor for an acute coronary syndrome in the young adult population and can even be used to prevent myocardial infarction in young adults [31]. In the present study, the TG/HDL-C ratio was also significantly higher in young nondiabetic patients with CHD when compared to those without CHD.

Gender differences proved to exist in the development of CHD. Male gender was known to have a greater risk of developing CVD than women due to the protective effect of hormones, as long as women are of childbearing age. As shown in our study, 85.0% of CHD patients were men. Whether there were gender differences of lipid profiles in CHD is still rarely reported, especially in those young adults. The results of the present study indicated that in those nondiabetic men younger than 65 years of age, the level of HDL-C might be associated with the risk of CHD, and with the decline of the level of HDL-C, the severity of coronary artery disease increased. However, the TG/HDL-C ratio showed no significant differences even though it was higher in the CHD group. We deemed that this might be related to the small sample size. In addition, all the lipid parameters were comparable between the CHD group and normal group in women. These might be due to the protective effect of hormones. Sample size should be also considered. More data are needed to confirm it.

5. Conclusions

Dyslipidemia is one of the most recognized risk factors associated with CHD, and many lipid parameters were demonstrated related to the occurrence of CHD; however, they may fall short when determining the definite cardiovascular risk in young adults. Our study suggests that HDL-C may be inversely associated with the risk of CHD in young nondiabetes CHD patients, especially in men. More research is needed to confirm it.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Ziyang Hu and Jingle Cui contributed equally to this work.

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Retraction

Retracted: Clinical Study on Long-Term Sinus Reversion Rate and Left Atrial Function Recovery of Mitral Valve Disease with Atrial Fibrillation under Modified Surgical Radiofrequency Ablation

Cardiology Research and Practice

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] J. Cui, Z. Hu, T. Li, Z. Guo, W. Luo, and Z. Huang, "Clinical Study on Long-Term Sinus Reversion Rate and Left Atrial Function Recovery of Mitral Valve Disease with Atrial Fibrillation under Modified Surgical Radiofrequency Ablation," *Cardiology Research and Practice*, vol. 2021, Article ID 5667364, 5 pages, 2021.

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Research Article

Clinical Study on Long-Term Sinus Reversion Rate and Left Atrial Function Recovery of Mitral Valve Disease with Atrial Fibrillation under Modified Surgical Radiofrequency Ablation

Jingle Cui,[1] **Ziyang Hu**,[2] **Tao Li**,[1] **Ziyang Guo**,[1] **Weiquan Luo**,[3] **and Zhiyong Huang**[3]

[1]*Department of Cardiothoracic Surgery, Hospital of Traditional Chinese Medicine of Zhongshan, ZhongShan City 528400, China*
[2]*Department of Cardiology, Hospital of Traditional Chinese Medicine of Zhongshan, ZhongShan City 528400, China*
[3]*Department of Ultrasound, Hospital of Traditional Chinese Medicine of Zhongshan, ZhongShan City 528400, China*

Correspondence should be addressed to Jingle Cui; lejingcui@163.com

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We aimed to study the long-term sinus reversion rate and recovery of left atrial function after modified surgical radiofrequency ablation for permanent atrial fibrillation caused by mitral valve disease. From March 2014 to May 2020, 35 patients who underwent modified surgical radiofrequency ablation during cardiac valve surgery in our hospital were selected as the study group, and 25 normal individuals without cardiac structural changes were selected as the control group. The time of modified surgical radiofrequency ablation and long-term sinus reversion rate were measured, and left atrial anteroposterior, superoinferior, left and right diameters, left atrial ejection fraction, left atrial filling index, and left atrial ejection force were measured before and 6 months after surgery. The mean ablation time was 23.2 min, and the long-term sinus reversion rate was 80.0%. The left atrium diameter decreased and the left atrium ejection fraction increased after the operation ($P < 0.05$). The left atrium filling index and ejection force were significantly increased in 28 patients with sinus reversion ($P < 0.05$). The decrease in left atrial diameter and the increase in left atrial ejection fraction were correlated with sinus conversion after surgery ($P < 0.05$). The modified operation is simple, the curative effect is definite, and the sinus reversion rate is high, which is beneficial to the restoration of left atrial structure, ejection function, and hemodynamic function.

1. Introduction

Atrial fibrillation is a common arrhythmia that is mostly secondary to valvular heart disease. Due to structural changes in the left atrium after valvular disease, atrial fibrillation often appears persistent. The main treatment for persistent atrial fibrillation is maze III surgery, with a success rate of 97%, but the operation is complex and traumatic [1]. Developments in technology have enabled radiofrequency ablation to be used instead of cutting and suturing. The ablation route is constantly improved and simplified, and the trauma is greatly reduced. The sinus reversion rate can reach 80–90% [2–4]. Studies have shown that atrial fibrillation has a great impact on left atrial function. In addition to structural measurement, mechanical ejection function, hemodynamics, and other indicators have been added to the detection of left atrial function [5–7]. Many studies have investigated the recovery of left atrial function in patients with paroxysmal atrial fibrillation after interventional ablation [8–11], but there are few reports on the recovery of left atrial function after surgical treatment of valvular disease combined with atrial fibrillation [12–14]. In this study, patients with valvular disease complicated by atrial fibrillation were selected as the study subjects. The modified ablation route and procedure was used to treat atrial fibrillation, while surgery was performed on the heart valve.

The effect of the modified procedure in shortening the operation time, ensuring a curative effect and the recovery of left atrial function, is discussed.

2. Materials and Methods

2.1. General Data. From March 2014 to May 2020, 35 patients with mitral valve disease combined with atrial fibrillation underwent mitral valve replacement or plasty and modified maze radiofrequency ablation in our hospital. There were 15 men and 20 women with an average age of 55 years (range, 40–69 years). There were 9 cases of simple mitral valve disease, 18 cases of mitral valve combined with tricuspid valve disease, and 8 cases of mitral valve, aortic valve, and tricuspid valve combined disease. Twenty-five healthy individuals without cardiac structural lesions were selected as the control group. All patients were diagnosed by transthoracic echocardiography before surgery, and left ventricular ejection fraction (LVEF) and left atrial function were measured. The patients were treated with digoxigenin, furosemide, and amiodarone for 1-2 weeks. This study was approved by Zhongshan Hospital of Traditional Chinese Medicine. Written informed consent was obtained from the patient.

2.2. Procedure and Radiofrequency Ablation Route. Catheter drainage of the superior vena cava and inferior vena cava was used to establish cardiopulmonary bypass. The right superior and inferior pulmonary vein entrances were ablated under parallel circulation. After cardiac arrest, the left atrium was examined. If a thrombus was present, the thrombus was removed first. The left superior and inferior pulmonary vein entrances were ablated. The left atrial appendage was then excised. The left atrial appendage to the left superior pulmonary vein was ablated, and the left atrial appendage stump was sutured. If a thrombus was found in the left atrial appendage or if the patient was elderly (over 65 years old), ablation was performed at the root of the left atrial appendage and from the right superior pulmonary vein to the root of the left atrial appendage. The left atrial appendage was closed in the left atrium without removal of the left atrial appendage. Next, ablation of the right superior pulmonary vein to the left superior pulmonary vein was performed. The right superior pulmonary vein to the left inferior pulmonary vein was then ablated with ablation forceps around the lateral side of the right inferior pulmonary vein. In the same way, the right superior pulmonary vein to the mitral annulus was ablated. Subsequently, coronary sinus to isthmus ablation was performed. The right atrial incision was sutured as the eighth line. Each ablation line was ablated two to three times (Figure 1). Valve surgery was performed after radiofrequency ablation. An epicardial temporary pacemaker was placed. The ablation equipment used was bipolar radiofrequency ablation forceps (AtriCure Inc.). Ablation energy and time were calculated by an ablation machine according to tissue thickness.

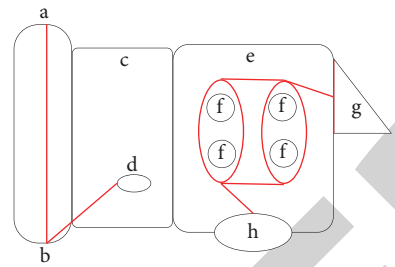

Figure 1: Graphical representation of procedure and radiofrequency ablation route. (a) Superior vena cava. (b) Inferior vena cava. (c) Right atrium. (d) Coronary sinus. (e) Left atrium. (f) Pulmonary venous orifice. (g) Left atrial appendage. (h) Mitral orifice.

2.3. Postoperative Treatment and Follow-Up. The patients were treated with vasoactive drugs to maintain hemodynamic stability and amiodarone to maintain sinus rhythm. An epicardial temporary pacemaker was set to 80 beats per minute to guarantee heart rate. The same drug treatment as before surgery was maintained until 3–6 months after surgery. Six months after the operation, the patients were followed up with electrocardiography and color Doppler ultrasonography. The LVEF, left atrial function including left atrial structure (anterior and posterior, upper and lower, left and right diameters), mechanical function (diastolic and systolic volumes of left atrium were measured by four-chamber echocardiography, and left atrial ejection fraction (LAEF) was calculated), E peak, A peak, and their velocity time integral were measured by color Doppler ultrasound. Left atrial filling index (LAFI) was defined as LAFI = A peak time velocity integral/(A peak time velocity integral + E peak time velocity integral), and left atrial ejection force (AEF) was defined as $\mathrm{AEF} = 0.5 \times \rho \times \mathrm{MVA} \times (\mathrm{VA})\ 2 \times 10 - 3$, where ρ is the viscosity coefficient $1.06/\mathrm{m}^3$, MVA is the area of mitral valve orifice (cm^2) measured using the pressure half-time method, VA is the A peak flow velocity of mitral valve orifice (cm/s), and the unit is kdynes [8]. At the same time, the left atrial function was measured in the 25 controls.

2.4. Statistical Methods. SPSS (version 16.0) was used to process the data. Statistical data were expressed as mean ± standard deviation. Statistical significance was set at $P < 0.05$.

3. Results and Discussion

3.1. Surgery. All patients underwent radiofrequency ablation of atrial fibrillation. In mitral valve replacement, mechanical valve replacement was performed in 18 cases, bioprosthetic valve replacement in 12 cases, and mitral valvuloplasty in 7 cases. The average postoperative discharge time was 19 days. All patients were followed up for 6 months. The mitral valve membrane worked well, without stenosis or regurgitation. During the follow-up period, there were no instances of need to install a permanent pacemaker, stroke, or thrombosis complications.

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The average ablation time was 23.2 min. Of 35 cases, 28 cases converted to sinus rhythm 6 months after the operation, and the cardioversion rate was 80%.

3.2. Left Atrial Structure and Function. The results showed that the left atrial anteroposterior diameter and superoinferior diameter were decreased ($P < 0.005$), and LAEF was increased ($P < 0.005$) (Table 1); there was no significant difference between left and right atrial diameters ($P = 0.139$), but the difference was shown in paired analysis ($P = 0.041$). There were significant differences in left atrial structure and LAEF before and after the operation in paired analysis ($P < 0.05$).

3.3. LAFI and Left AEF. Sinus rhythm was restored in 33 patients after treatment, and A peak was restored. The left atrial filling index and left AEF were calculated from A peak to evaluate left atrial hemodynamics. The LAFI and left AEF increased significantly after sinus reversion, but there was still a significant difference compared with the control group ($P < 0.05$) (Table 2).

3.4. Correlation Analysis. There was no significant correlation between the size of the preoperative structure and sinus reversion of atrial fibrillation. There was a correlation between the decrease in the left atrial superoinferior diameter and the increase in LAEF ($P < 0.05$) (Table 3).

4. Discussion

In structural heart disease, mitral valve disease often causes atrial fibrillation, which may be caused by an increase in left atrial load and blood stasis resulting from mitral stenosis, and the impact of high-speed systolic blood flow from the left ventricle is caused by mitral regurgitation, both of which eventually lead to the enlargement of the left atrial structure and the formation of multiple reentry pathways in the left atrium. The treatment of atrial fibrillation has changed from the traditional "cut and sew" Cox maze III procedure to current radiofrequency ablation. Among them, bipolar radiofrequency ablation is effective with fewer side effects, and the ablation circuit is constantly improved. The maze radiofrequency ablation in this study followed the Cox maze III procedure; except that, while the right atrial longitudinal incision was "cut and sew" and the ablation route was simplified, the rest of the lines were radiofrequency ablation. Using this improved method, the right lower pulmonary vein incision can be omitted in the operation. Most patients had the left atrial appendage in the heart sutured, which reduced the risk of bleeding. The shortening of operation time plays an important role in myocardial protection and prevention of ischemia-reperfusion injury [15], and microvessels play an important role in myocardial protection [16, 17]. Studies have shown that mitochondrial homeostasis and quality promote myocardial protection [18–20] and reduce myocardial injury [21, 22]. In general, the improved operation method has an improved outcome, simpler operation, shorter operation time, and less frequent bleeding complications than the traditional method.

With the development of atrial fibrillation research, increasing attention has been paid to the role of left atrial function in cardiac function. Atrial fibrillation makes left atrial autonomic systolic function disappear, reducing the length of the left ventricular diastolic period, resulting in a change in cardiac stroke output, which affects the stability of hemodynamics, and leads to a decline in cardiac function. In the past, left atrial function was evaluated using echocardiography only in the structure. In recent years, the study of the left atrial function has changed from simple structure measurement to mechanical ejection function and hemodynamics. In this study, we measured the anterior and posterior diameters of the left atrium in the long axis view of the left heart, superior and inferior diameters, and left and right diameters of the left atrium in the four-chamber view. The LAEF was calculated from the changes in left atrial diastolic and systolic volume in the four-chamber view, the LAFI was calculated from the proportion of A peak area to evaluate the role of left atrial active contraction in the whole left ventricular diastolic period, and the left AEF was calculated from the maximum A peak velocity and mitral orifice area to infer the left atrial active systolic force. The above method is simple and can be used to evaluate left atrial function from multiple perspectives. However, there is no comprehensive index to evaluate left atrial function, and the LAEF is considered to be a more intuitive index.

With respect to left atrial structure and function recovery, paired analysis showed that the left atrial structure and LAEF improved in the long term after the modified ablation. Recovery of the A peak is very important for the evaluation of left atrial hemodynamics. Compared with the patients without cardioversion, the left atrial structure and ejection function of the patients with cardioversion were better, and the left atrial filling index and left AEF were also significantly increased. Some studies have shown that the left atrial function of pure atrial fibrillation can return to normal after interventional radiofrequency ablation [8–11], but that the left atrial function of valvular fibrillation cannot be restored after surgical ablation. The reason is that the left atrial structure of the former has no obvious change, while the left atrial structure of the latter has been enlarged due to the long-term volume overload caused by mitral valve disease. In our study, there was a certain difference from the normal group, indicating that the structural change in the left atrium caused by valvular disease is a chronic remodeling process; although mitral valve disease has been treated and sinus rhythm has been restored, left atrial structure and function are still difficult to return to normal levels. From the correlation analysis, we can see that the more obvious the change in left atrial structure, the lower the possibility of cardioversion. Therefore, the success rate of cardioversion can be predicted by changes in the left atrial structure. In view of the limited number of cases in this study, more cases and further data analysis are needed to support this conclusion.

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Table 1: Comparison of left atrial structure and ejection fraction before and 6 months after operation.

	Before operation	6 months after operation	Normal group
Anteroposterior diameter (mm)	51.2 ± 9.2	45.0 ± 8.3 ($P < 0.005$)	36.8 ± 3.4
Superoinferior diameter (mm)	71.7 ± 12.4	59.7 ± 10.0 ($P < 0.005$)	48.0 ± 4.9
Left-right diameter (mm)	53.6 ± 15.0	49.2 ± 8.9 ($P = 0.041$)	37.2 ± 3.1
LAEF (%)	19.15 ± 7.9	26.1 ± 8.4 ($P < 0.005$)	55.9 ± 7.2

Table 2: Left atrial filling index and left atrial ejection force in the sinus reversion group.

	Postoperative sinus reversion group	Normal group
LAFI (%)	18.6 ± 9.1	36.8 ± 7.5
Left AEF (kdynes)	6.0 ± 4.5	9.7 ± 5.0

Table 3: Correlation analysis of postoperative sinus recovery, left atrial structure, and left atrial ejection fraction.

	Anteroposterior diameter	Superoinferior diameter	Left-right diameter	LAEF
Correlation coefficient	−0.158	−0.288*	−0.219	0.290*
P	0.273	0.045	0.131	0.041

Kendall correlation analysis. $P < 0.05$, statistical difference. *Statistical significance.

5. Conclusions

In general, modified surgical radiofrequency ablation is simple, the curative effect is definite, and the sinus reversion rate is high, which is beneficial to the restoration of left atrial structure, ejection function, and hemodynamic function. The modified operation is worth clinical promotion.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Jingle Cui and Ziyang Hu equally contributed to this study.

Acknowledgments

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Retraction

Retracted: Development and Validation of a Risk Prediction Model for Ventricular Arrhythmia in Elderly Patients with Coronary Heart Disease

Cardiology Research and Practice

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In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

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[1] Y. Dong, Y. Shi, J. Wang et al., "Development and Validation of a Risk Prediction Model for Ventricular Arrhythmia in Elderly Patients with Coronary Heart Disease," *Cardiology Research and Practice*, vol. 2021, Article ID 2283018, 12 pages, 2021.

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Research Article

Development and Validation of a Risk Prediction Model for Ventricular Arrhythmia in Elderly Patients with Coronary Heart Disease

Ying Dong,[1] **Yajun Shi**,[1] **Jinli Wang**,[1] **Qing Dan**,[1] **Ling Gao**,[1] **Chenghui Zhao**,[1] **Yang Mu**,[1] **Miao Liu**,[2] **Chengliang Yin**,[3,4,5] **Rilige Wu**,[4] **Yuqi Liu**,[1] **Yang Li**,[1] **and Xueping Wang**[1]

[1]*Department of Cardiology, First Medical Center of Chinese PLA General Hospital, Beijing, China*
[2]*Graduate School of Chinese PLA General Hospital, Beijing, China*
[3]*National Engineering Laboratory for Medical Big Data Application Technology, Chinese PLA General Hospital, Beijing, China*
[4]*Medical Big Data Research Center, Medical Innovation Research Division of Chinese PLA General Hospital, Beijing, China*
[5]*Faculty of Medicine, Macau University of Science and Technology, Macau, China*

Correspondence should be addressed to Yang Li; liyangbsh@163.com and Xueping Wang; wangxueping@mode301.cn

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Background. Sudden cardiac death is a leading cause of death from coronary heart disease (CHD). The risk of sudden cardiac death (SCD) increases with age, and sudden arrhythmic death remains a major cause of mortality in elderly individuals, especially ventricular arrhythmias (VA). We developed a risk prediction model by combining ECG and other clinical noninvasive indexes including biomarkers and echocardiology for VA in elderly patients with CHD. *Method*. In the retrospective study, a total of 2231 consecutive elderly patients (≥60 years old) with CHD hospitalized were investigated, and finally 1983 patients were enrolled as the model group. The occurrence of VA within 12 months was mainly collected. Study parameters included clinical characteristics (age, gender, height, weight, BMI, and past medical history), ECG indexes (QTcd, Tp-e/QT, and HRV indexes), biomarker indexes (NT-proBNP, Myo, cTnT, CK-MB, CRP, K^+, and Ca^{2+}), and echocardiology indexes. In the respective study, 406 elderly patients (≥60 years old) with CHD were included as the verification group to verify the model in terms of differentiation and calibration. *Results*. In the multiparameter model, seven independent predictors were selected: LVEF, LAV, HLP, QTcd, sex, Tp-e/QT, and age. Increased HLP, Tp-e/QT, QTcd, age, and LAV were risk factors (RR > 1), while female and increased LVEF were protective factors (RR < 1). This model can well predict the occurrence of VA in elderly patients with CHD (for model group, AUC: 0.721, 95% CI: 0.669~0.772; for verification group, AUC: 0.73, 95% CI: 0.648~0.818; Hosmer–Lemeshow $\chi^2 = 13.541$, $P = 0.095$). After adjusting the predictors, it was found that the combination of clinical indexes and ECG indexes could predict VA more efficiently than using clinical indexes alone. *Conclusions*. LVEF, LAV, QTcd, Tp-e/QT, gender, age, and HLP were independent predictors of VA risk in elderly patients with CHD. Among these factors, the echocardiology indexes LVEF and LAV had the greatest influence on the predictive efficiency of the model, followed by ECG indexes, QTcd and Tp-e/QT. After verification, the model had a good degree of differentiation and calibration, which can provide a certain reference for clinical prediction of the VA occurrence in elderly patients with CHD.

1. Introduction

Sudden cardiac death is a leading cause of death from coronary heart disease (CHD). Sudden cardiac death affects approximately 3 million people worldwide each year, more than the deaths from breast, lung, and colon-rectum cancers combined [1]. The risk of sudden cardiac death (SCD) increases with age, and sudden arrhythmic death remains a major cause of mortality in elderly individuals [2]. Although SCD can occur due to a slow heart rhythm (bradycardia) caused by stopping or blocking of the normal sinus pacemaker, more commonly, it is due to a rapid heart rhythm (tachycardia), usually

originating in the ventricles—ventricular tachycardia (VT) or ventricular fibrillation (VF) [3]. Studies indicate that 50%–85% of sudden cardiac deaths are attributed to ventricular arrhythmias (VA) [4, 5].

Due to myocardial ischemia and partial myocardial tissue necrosis or fibrosis in patients with CHD, abnormal cardiac electrophysiological remodeling occurs, which is easy to induce VA. ECG indexes can reflect the electrophysiological changes of the heart. Although there were some studies that incorporate ECG indexes into the prediction model of clinical events [6–10], there was still a lack of large sample research on the combination of multiple ECG parameters for VA in elderly patients with CHD. Previous researches paid more attention to the relationship of one single ECG index and VA [11, 12], while myocardial electrical activity is actually influenced by multifactors. One single ECG index is far from enough to reflect the myocardial electrical activity.

The aim of this study was, therefore, to develop a risk prediction model by combining ECG and other clinical noninvasive indexes including biomarkers and echocardiology for VA in elderly patients with CHD. We first retrospectively investigated the relationship between various indexes and VA in elderly CHD patients, hoping to establish a model to predict VA. Then, we prospectively collected data to verify the model in terms of differentiation and calibration.

2. Methods

2.1. Study Population. Originally, a total of 2231 consecutive elderly patients (≥60 years old) with CHD hospitalized at Chinese PLA General Hospital from January 2010 to December 2016 were investigated retrospectively. The occurrence of VA within 12 months was mainly collected. The patients with no complete clinical information were excluded. Finally, 1983 patients who had complete data were enrolled as the model group.

A total of 513 elderly patients (≥60 years old) with CHD who were hospitalized in the same unit from January 2017 to December 2018 were included as the verification group. The results of a 24-hour ambulatory electrocardiogram were collected respectively at the first hospitalization, 6 months, and 12 months after hospitalization. The occurrence of VA events was observed. Finally, 406 patients with complete data were included.

Inclusion criteria for the subjects were as follows: aged over 60 years; clinically diagnosed as CHD. In both the model group and verification groups, we excluded patients with secondary ST-T changes caused by various causes, such as congenital heart disease, valvular heart disease, cor pulmonale, hypertensive heart disease, preexcitation syndrome, intraventricular conduction block, and pacemaker implantation. In addition, patients who have taken amiodarone or long-term chemotherapeutic drugs within one month, which may affect the QT interval and T-wave morphology, were also excluded [13, 14].

All the patients signed informed consent forms, and the study complied with the Declaration of Helsinki and was approved by the Research Ethics Board of our center.

2.2. Electrocardiogram Measurement. Electrocardiography used a standard digital recorder (GE, MAC 5500) with 12 simultaneous leads at a paper speed of 25 mm/s.

2.2.1. QTcd. Upon each lead, a smooth and clear baseline for 3 consecutive QT intervals was measured, and the mean value was calculated [15]. In order to eliminate the effect of heart rate on the results, the Bazzett formula was used to correct the QT interval, and the correction value was QTc: $QTc = QT/\sqrt{RR}$. QTc_{max} and the QTc_{min} were selected in the synchronous standard 12-lead ECG, and then QTcd was obtained: $QTcd = QTc_{max} - QTc_{min}$.

2.2.2. Tp-e. Tp-e was measured in three consecutive cardiac cycles, and the mean values were calculated [16]. Tp-e was defined as the interval from the peak of a positive T-wave or the nadir of a negative T-wave to the end of the T-wave. The QT interval of lead V3 was measured and the correction value QTc was calculated. Tp-e and QTc values were input into the computer, and the Tp-e/QTc ratio was calculated. All ECG measurements were performed independently by two physicians blindly. When the measurement results were inconsistent, the average was calculated.

2.3. Ventricular Arrhythmias. A 24 h 12-lead dynamic electrocardiograph was used for data acquisition, including heart rate variability (HRV) indexes and VA. The range of VA included [17] cardiac arrhythmia ≥3 consecutive complexes originating in the ventricles at a rate of >100 bpm (cycle length: <600 ms), torsades de pointes, ventricular flutter, and ventricular fibrillation.

3. Statistical Analyses

In univariate analysis, the categorical variables were expressed by frequency and percentage, and Pearson's chi-square test or Fisher's exact test were used for comparison between groups. The continuous variables were expressed by mean ± standard deviation (SD), and independent-sample t test or rank sum test was used for comparison between groups. The variables with P value <0.1 were further involved in multivariate analysis. The Kaplan–Meier method was used to build the survival curves, and Cox regression was used for multivariate analysis. The test levels for entry and elimination of variables were, respectively, set at 0.05 and 0.10. The accuracy of the prediction model was evaluated by area under ROC curve (AUC). Based on the results of multivariate analysis, a nomogram was established. The C-index was used to verify the nomogram, and the test level $\alpha = 0.05$. The verification group's data were put into the established prediction model to calculate the prediction results. The area under ROC curve was used to evaluate the differentiation degree of the model, and Hosmer–Lemeshow goodness-of-fit was used to test the calibration of the evaluation model. Ninety-five percent confidence intervals (95% CI) of hazard ratio (HR) were used as common measures to assess relative risk. All statistical analysis were

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performed using SPSS statistics 19.0 and R program (version 3.6.2). $P < 0.05$ were considered statistically significant.

4. Results

4.1. Demographic and Clinical Characteristics of the Model Group. The demographic and clinical characteristics of all subjects are presented in Table 1. The average age of all patients was (74.09 ± 9.00) years, including 772 patients aged 60–69 years (38.93%), 583 patients aged 70–79 years (29.40%), 597 patients aged 80–89 years (30.11%), and 31 patients over 90 years (1.56%). There were 1293 male patients (65.20%) with an average age of (74.30 ± 9.23) years and 690 female patients (34.80%) with an average age of (73.69 ± 8.53) years. The follow-up period was 12 months. 124 patients with VA (6.25%) were reported, and the average occurrence time was (7.9 ± 4.4) months. VA events included 14 cases of ventricular fibrillation, 1 case of pleomorphic ventricular tachycardia, 1 case of frequent ventricular tachycardia implanted with ICD, and other 108 cases of monomorphic ventricular tachycardia.

In terms of baseline data, the proportions of males, smoking, drinking, diabetes, and hyperlipidemia (HLP) in the VA group were higher than those in the non-VA group. In terms of ECG indexes, QTcd and Tp-e/QT in the VA group were higher than those in the non-VA group, and the SDNN index in HRV was lower than that in the non-VA group. In terms of biomarker indexes, NT-proBNP, Myo, cTnT, CK-MB, and CRP in VA group were higher than those in the non-VA group, while Ca^{2+} concentration in VA group was lower than that in the non-VA group. In terms of echocardiology, there were significant differences in left ventricular ejection fraction (LVEF), left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), left atrial anterior-posterior diameter, left atrial superior-inferior diameter, left atrial left-right atrial diameter, and right atrial diameter (RAD) between the two groups. LVEF in the VA group was lower than that in the non-VA group, while the other indexes in the VA group were higher than those in the non-VA group.

4.2. Screening of Independent Predictors of VA. The risk factors affecting VA were screened by univariate analysis, and the variables with P value less than 0.1 were further involved in multivariate analysis. All the factors were analyzed by collinearity test, and the factors with collinearity did not enter into the multifactor analysis. Among the factors, age, Tp-e/QT, and NT-proBNP entered the multivariate analysis in the form of quartile. cTnT was more specific and sensitive than Myo and CK-MB in the diagnosis of myocardial injury in patients with acute myocardial infarction and heart failure [18], so cTnT was selected for multivariate analysis. Left atrial volume (LAV) was calculated by the combination of left atrial anterior-posterior diameter, left atrial superior-inferior diameter, and left-right atrial diameter (LAV ml = 4/3 π ∗ (left atrial anterior – posterior diameter mm/2) ∗ (left atrial superior-inferior diameter mm/2) ∗ (left atrial left-right diameter mm/2)/1000). The assignment of classification variables is described in Table 2, and the first level of the variable was defined as the base of comparison. Finally, gender, age (quartile), smoking, drinking, diabetes, HLP, QTcd, Tp-e/QT (quartile), SDNN, NT-proBNP (quartile), cTnT, Ca^{2+}, LVEF, and LAV were selected for the Cox regression model. A forward stepwise regression method was used. The results showed that gender, age, HLP, QTcd, Tp-e/QT, LVEF, and LAV were independently correlated with the occurrence of VA. Age and Tp-e/QT were dumb variables with the first quartile as the baseline ($P < 0.05$). The cumulative survival rate of all patients at the 12th month was between 93% and 94% (Figure 1). The time-dependent ROC curve of the model was drawn, and the AUC was 0.721 (95% CI: 0.669~0.772) (Table 3 and Figures 2 and 3).

4.3. Comparison of Four Cox Regression Models including Different Factors. We selected different combinations of factors to establish Cox regression models for VA. The AUC of each model was compared, and the results are shown in Table 4 and Figure 4. The model's risk prediction probability was increased by 2.12% after adding ECG indexes to the prediction model, which included clinical baseline data, biomarker indexes and echocardiology indexes. The model's risk prediction probability was increased by 28.75% after adding the echocardiology indexes, which included clinical baseline data, ECG indexes, and biomarker indexes. The model's risk prediction probability was increased by 1.26% after adding the biomarker indexes, which included clinical baseline data, ECG indexes, and echocardiology indexes. Therefore, the Cox regression model with all types of factors had the highest prediction probability, in which echocardiology indexes had the greatest influence on the prediction efficiency, followed by ECG indexes (Table 4 and Figure 4).

4.4. Establishment of Nomogram. To simplify the complex model formula, we established a nomogram based on seven independent variables selected by the Cox regression model which included gender, age, HLP, QTcd, Tp-e/QT, LVEF, and LAV. Each factor had a score, and the total scores could be calculated (1.4–9.4) with the corresponding risk probability range 1-0. The C-index of the nomogram for predicting the overall risk of non-VA in 1 year was 0.785, suggesting that the nomogram had a good predictive value for the event (Figure 5).

4.5. Cox Regression Model Verification. Among 406 patients of the verification group, there were 40 patients with ventricular arrhythmias (9.85%). No significant difference was observed in gender, age, HLP, QTcd, Tp-e/QT, LVEF, and LAV between the model group and verification group (Table 5). Data of the verification group were substituted into the established Cox regression model, and the corresponding risk prediction probability value of each patient was calculated using the following equation:

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Table 1: Comparison of demographic and clinical characteristics between VA and non-VA groups.

Characteristic	VA ($N = 124$)	Non-VA ($N = 1859$)	z/χ^2	P value
Male, *n* (%)	103 (83.06%)**	1190 (64.01%)	18.597	$P \leq 0.001$
Age, mean (SD), y	75.44 (8.70)	74.00 (9.01)	−1.770	0.077
Height, mean (SD), cm	167.61 (6.64)**	165.08 (7.69)	−3.708	$P \leq 0.001$
Weight, mean (SD), kg	69.33 (12.29)	68.00 (11.19)	−1.807	0.071
BMI, mean (SD), kg/m^2	24.60 (3.80)	24.87 (3.45)	−0.438	0.662
Smoking, *n* (%)	48 (38.7%)*	570 (30.66%)	3.510	0.040
Drinking, *n* (%)	31 (25%)*	334 (17.97%)	3.829	0.036
Diabetes, *n* (%)	60 (48.39%)**	673 (36.20%)	7.407	0.005
Hypertension, *n* (%)	88 (70.97%)	1346 (72.40%)	0.120	0.399
HLP, *n* (%)	94 (75.81%)**	1083 (58.26%)	14.840	$P \leq 0.001$
Atherosclerosis, *n* (%)	14 (11.29%)	222 (11.94%)	0.047	0.483
QTcd, mean (SD), ms	37.77 (27.61)**	27.27 (18.47)	−4.313	$P \leq 0.001$
Tp-e/QT, mean (SD)	0.23 (0.04)**	0.21 (0.04)	−3.858	$P \leq 0.001$
SDNN, mean (SD), ms	91.99 (32.35)**	103.90 (38.36)	−3.744	$P \leq 0.001$
SDANN, mean (SD), ms	98.06 (48.02)	102.36 (50.91)	−1.529	0.126
RMSSD, mean (SD), ms	43.26 (38.05)	38.83 (37.84)	−0.931	0.352
PNN50 (%), mean (SD)	4.69 (6.15)	4.76 (7.67)	−0.502	0.615
NT-proBNP, mean (SD), pg/ml	1730.94 (4704.69)**	891.08 (3251.88)	−4.452	$P \leq 0.001$
Myo, mean (SD), ng/ml	133.57 (336.15)*	46.94 (101.67)	−2.445	0.014
cTnT, mean (SD), ng/ml	0.35 (0.97)**	0.22 (1.69)	−6.343	$P \leq 0.001$
CK-MB, mean (SD), ng/ml	10.88 (18.58)**	8.23 (23.66)	−4.058	$P \leq 0.001$
CRP, mean (SD), mg/dl	0.90 (2.45)*	0.61 (1.81)	−2.403	0.016
K^+, mean (SD), mmol/L	3.88 (0.40)	3.90 (0.42)	−0.551	0.582
Ca^{2+}, mean (SD), mmol/L	2.20 (0.10)**	2.24 (0.13)	−3.173	0.002
LVEF, mean (SD), %	49.50 (11.63)**	58.95 (7.66)	−9.334	$P \leq 0.001$
Interventricular septal thickness, mean (SD), mm	10.71 (1.37)	10.93 (1.37)	−1.218	0.223
LVPW, mean (SD), mm	10.08 (0.96)	10.11 (1.05)	−0.027	0.979
LVEDD, mean (SD), mm	48.40 (6.10)**	45.36 (4.89)	−5.640	$P \leq 0.001$
LVESD, mean (SD), mm	35.55 (7.11)**	31.07 (4.91)	−7.373	$P \leq 0.001$
Left atrial anterior and posterior diameter, mean (SD), mm	36.75 (5.21)**	35.33 (4.51)	−3.087	0.001
Left atrial superior and inferior diameter, mean (SD), mm	55.06 (5.53)**	51.47 (5.69)	−6.484	$P \leq 0.001$
Left atrial left and right atrial diameter, mean (SD), mm	38.54 (4.26)**	36.18 (4.42	−5.744	$P \leq 0.001$
E-peak, mean (SD), m/s	0.68 (0.20)	0.69 (0.21)	−0.208	0.835
A-peak, mean (SD), m/s	0.90 (0.26)	0.90 (0.23)	−1.897	0.058
Inner diameter of ascending aorta, mean (SD), mm	31.46 (3.79)	32.13 (3.57)	−1.560	0.119
Stroke volume, mean (SD), ml	52.17 (14.49)	55.30 (13.29)	−1.863	0.063
Internal diameter of right atrium, mean (SD), mm	35.50 (4.98)**	32.77 (4.25)	−5.507	$P \leq 0.001$

LVPW: left ventricular posterior wall; *means comparison between the two groups $P < 0.05$, **means comparison between the two groups $P < 0.01$.

Table 2: Variable assignment description.

Variable name	Variable type	Classified variable coding
Gender	2 classification	Male = 0, Female = 1
Age, year (quartile)	Ordered grade	60~66 year = 1 67~75 year = 2 76~82 year = 3 Above 82 year = 4
Smoking	2 classification	Nonsomker = 0, smoker = 1
Drinking	2 classification	Nondrinker = 0, drinker = 1
Diabetes	2 classification	Nondiabetes = 0, diabetes = 1
HLP	2 classification	Non-HLP = 0, HLP = 1
QTcd (ms)	Continuous variable	
Tp-e/QT (quartile)	Ordered grade	0~0.192 = 1 0.1921~0.224 = 2 0.2241~0.245 = 3 Above 0.245 = 4

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Table 2: Continued.

Variable name	Variable type	Classified variable coding
SDNN	Continuous variable	
NT-proBNP, pg/ml (quartile)	Ordered grade	0~63.01 = 1 63.02~171.4 = 2 171.41~474.1 = 3 Above 474.1 = 4
cTnT (ng/ml)	Continuous variable	
Ca^{2+} (mmol/L)	Continuous variable	
LVEF (%)	Continuous variable	
LAV (ml)	Continuous variable	

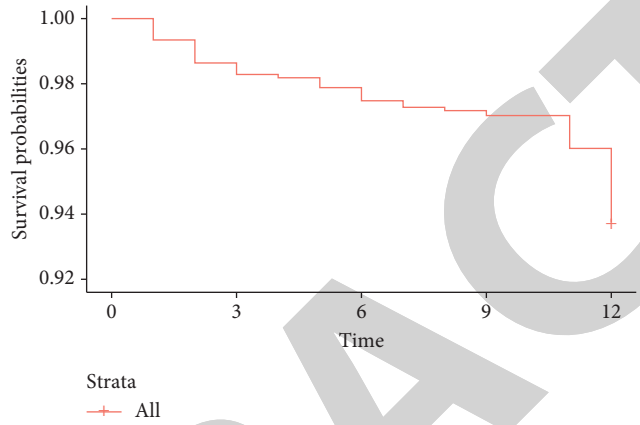
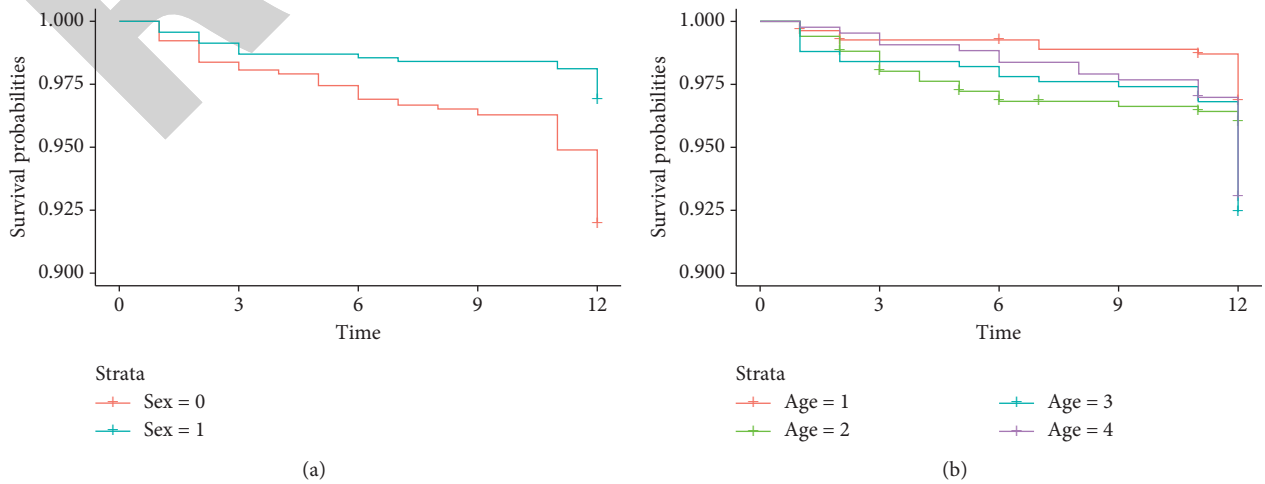


Figure 1: The cumulative survival rate of all patients in 12 months.

Table 3: Multivariate analysis of model group by Cox regression.

Variable code	Variable	B	SE	Wald	P value	HR (95% CI)
X_1	Sex	−0.913	0.246	13.830	$P \leq 0.001$	0.401 (0.248–0.649)
X_2^{**}	Age (2)	0.647	0.270	5.744	0.017	1.910 (1.125–3.241)
X_2^{***}	Age (3)	0.009	0.301	0.001	0.975	1.009 (0.560–1.820)
X_2^{****}	Age (4)	0.672	0.279	5.808	0.016	1.959 (1.134–3.384)
X_3	HLP	1.832	0.234	61.474	$P \leq 0.001$	6.245 (3.951–9.872)
X_4	QTcd	0.011	0.004	8.940	0.003	1.011 (1.004–1.018)
X_5^{**}	Tp-e/QT (2)	0.465	0.308	2.283	0.131	1.592 (0.871–2.910)
X_5^{***}	Tp-e/QT (3)	0.687	0.303	5.136	0.023	1.988 (1.097–3.601)
X_5^{****}	Tp-e/QT (4)	0.890	0.303	8.644	0.003	2.435 (1.345–4.408)
X_6	LVEF	−0.121	0.009	165.20	$P \leq 0.001$	0.886 (0.870–0.902)
X_7	LAV	0.016	0.007	5.268	0.022	1.016 (1.002–1.030)



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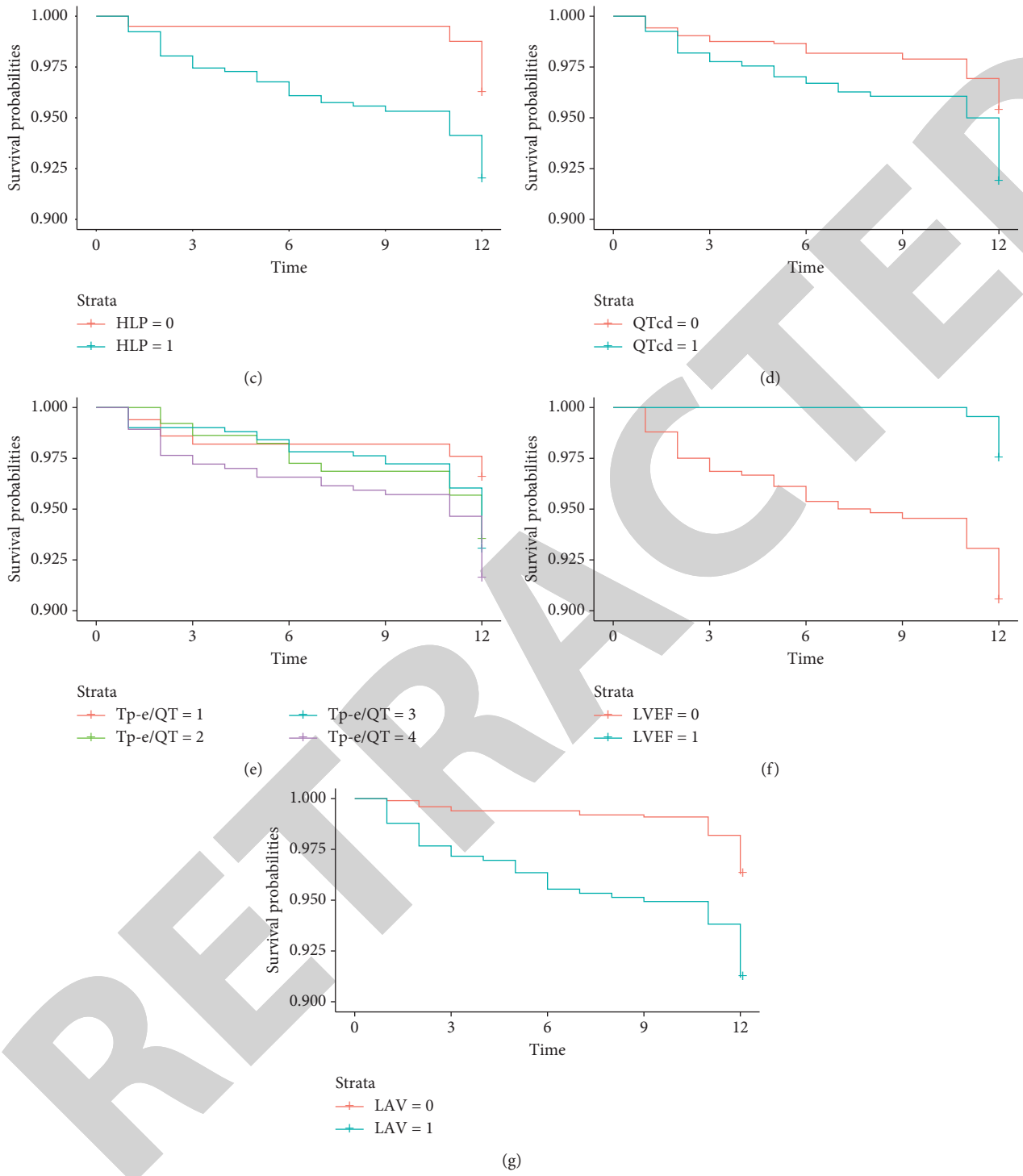

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Figure 2: Cumulative survival function curves of each classified variable (a)–(g). Indexes are grouped by median (d, f, g). (a) Cumulative survival function curve of gender. (b) Cumulative survival function curve of age. (c) Cumulative survival function curve of HLP. (d) Cumulative survival function curve of QTcd. (e) Cumulative survival function curve of Tp-e/QT. (f) Cumulative survival function curve of LVEF. (g) Cumulative survival function curve of LAV.

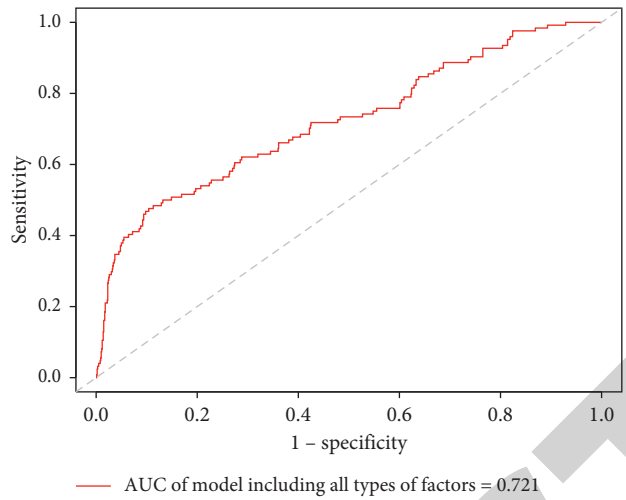

Figure 3: ROC curve of the model group.

Table 4: Comparison of AUC of each model.

Test variables	AUC (95% CI)	Standard error	P value
All types of factors	0.721 (0.669–0.772)	0.026	$P \leq 0.001$
Factors except ECG indexes	0.706 (0.652–0.761)	0.028	$P \leq 0.001$
Factors except echocardiology indexes	0.560 (0.504–0.616)	0.029	0.025
Factors except biomarker indexes	0.712 (0.659–0.756)	0.027	$P \leq 0.001$

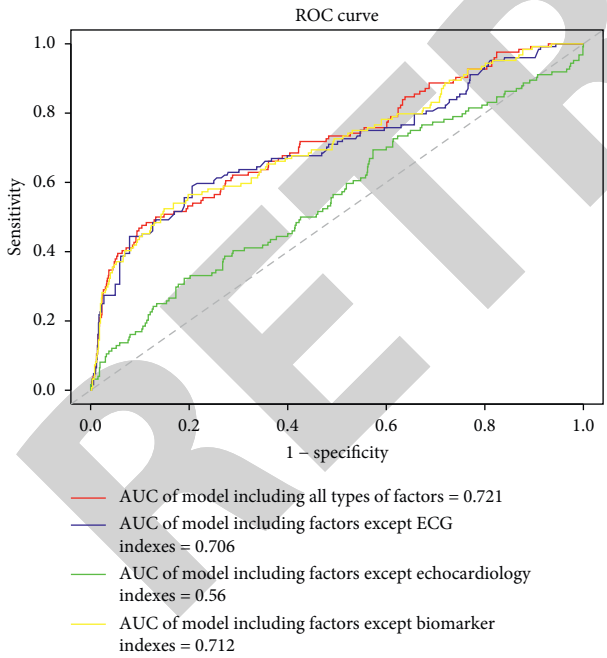

Figure 4: AUC comparisons of each model.

$$\hat{p} = 1 - S_0(t)^{\exp\left(\sum_{i=1}^{p}\beta_i X_i - \sum_{i=1}^{p}\beta_i \overline{X}_i\right)}. \quad (1)$$

According to the risk prediction probability value, the ROC curve of the verification group was drawn, with AUC 0.73 (95% CI: 0.648~0.818), indicating that the model had a certain distinguishing ability (Figure 6).

Calibration of the prediction model was evaluated by Hosmer–Lemeshow goodness-of-fit test. The prediction probability was sorted from small to large and divided into 10 groups according to ten points. The actual occurrence number and model prediction number of each group were calculated, respectively, and the actual incidence rate and predicted incidence rate were also calculated (Table 6). The actual incidence rate was expressed in the form of a bar chart, and the predicted incidence rate was expressed in the form of a curve (Figure 7). The results suggested that there was no statistical difference between predicted incidence rate and actual incidence rate (Hosmer-Lemeshow $\chi^2 = 13.541$, $P = 0.095$). The predictive model had a good calibration.

5. Discussion

Despite the progress in risk prediction of VA [19], there has been no generally accepted large-sample-calculated model for predicting the occurrence of VA in elderly patients with CHD so far. Golukhova et al. [10] assessed the prognostic association of numerous biomarkers associated with future development of malignant ventricular arrhythmia (MVA) in patients with coronary artery disease (CAD) in a prospective, single-center observational cohort evaluation including 108 patients. They reported that prior MVA or syncope (OR: 11.1; 95% CI: 2.8–44.4; $P < 0.01$), abnormal heart rate turbulence (HRT) (OR:13.6; 95% CI: 2.8–66.1; $P < 0.01$), and elevated plasma BNP (OR:14.3; 95% CI: 3.2–65.0; $P < 0.01$) were independent MVA predictors. However, they did not discuss the predictive efficiency of the model. Compared with their study, larger-sized samples were enrolled and

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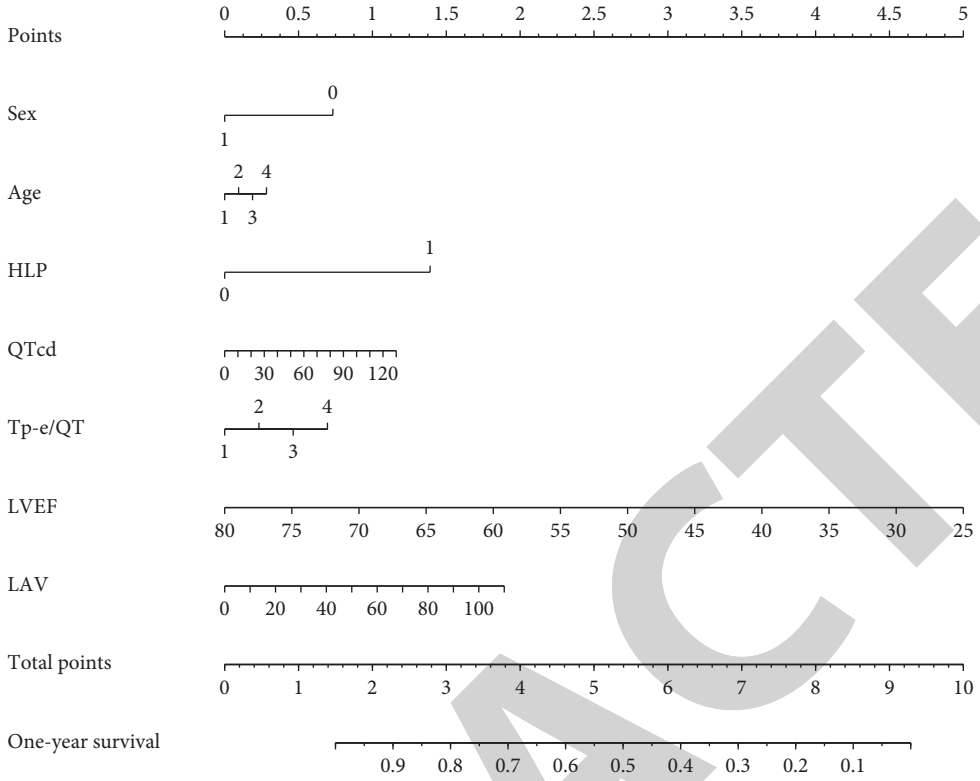

Figure 5: Nomogram for predicting the overall risk of non-VA in 1 year.

Table 5: Comparison of risk factors between model group and verification group.

	Model group ($N = 1983$)	Verification group ($N = 406$)	P value
Gender (male)	1293 (65.20%)	270 (66.50%)	0.668
Age			0.374
60~66 years	544 (27.43%)	120 (29.56%)	
67~75 years	506 (25.52%)	99 (24.38%)	
76~82 years	502 (25.32%)	66 (16.26%)	
Above 82 years	431 (21.73%)	121 (29.8%)	
HLP	1177 (59.35%)	225 (55.42%)	0.145
QTcd (ms)	27.92 ± 19.33	28.40 ± 20.41	0.885
Tp-e/QT			0.266
0~0.19	500 (25.21%)	63 (15.52%)	
0.20~0.22	510 (25.72%)	92 (22.66%)	
0.23~0.24	506 (25.52%)	121 (29.8%)	
Above 0.24	467 (23.55%)	130 (32.02%)	
LVEF (%)	58.24 ± 8.38	58.58 ± 8.38	
LAV (ml)	35.59 ± 11.34	34.67 ± 10.43	0.259

prospective model verification was performed in our study. Besides, we also compared the effects of different types of noninvasive indexes on the prediction performance of the model.

In this study, we established a multiparameter model for predicting VA in elderly patients with CHD and further verified its efficiency. Seven independent predictors, in order of importance of the relationship with outcome events, LVEF, LAV, HLP, QTcd, sex, Tp-e/QT, and age, were selected. Increased HLP, Tp-e/QT, QTcd, age, and LAV were risk factors (RR > 1), while female and increased LVEF were protective factors (RR < 1). This model can well predict the occurrence of VA in elderly patients with CHD (for model group, AUC: 0.721, 95% CI: 0.669~0.772; for verification group, AUC: 0.73, 95% CI: 0.648~0.818; Hosmer-Lemeshow $\chi^2 = 13.541$, $P = 0.095$). In addition, we compared the prediction performance of different parameters. After adjusting the predictors, it was found that the combination of clinical indexes and ECG indexes could predict VA more efficiently than using clinical indexes alone.

VA is related to ventricular dysfunction and the extent of coronary disease. Among the echocardiography indexes, LVEF can accurately evaluate the ventricular function of patients with heart failure caused by various causes, and it is

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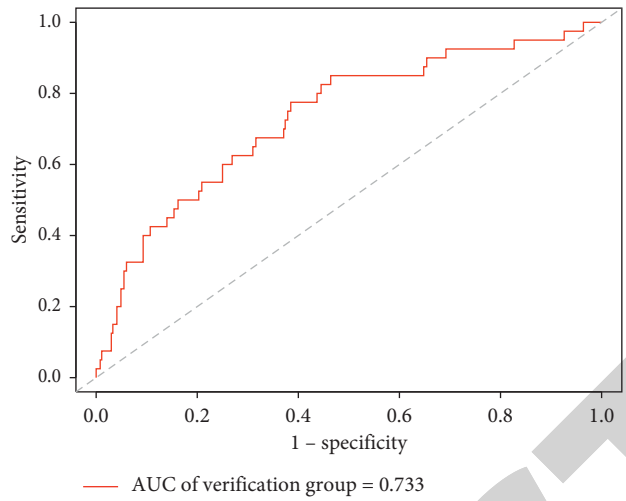

Figure 6: ROC curve of verification group.

Table 6: Actual incidence rate and predicted incidence rate.

Tenth quantile	Predicted incidence rate (%)	Actual incidence rate (%)
1	0.44	0
2	0.75	2.01
3	1.02	0
4	1.34	2.53
5	1.71	0
6	2.11	2.01
7	2.60	3.03
8	3.31	4.04
9	4.75	5.56
10	44.8	43.65

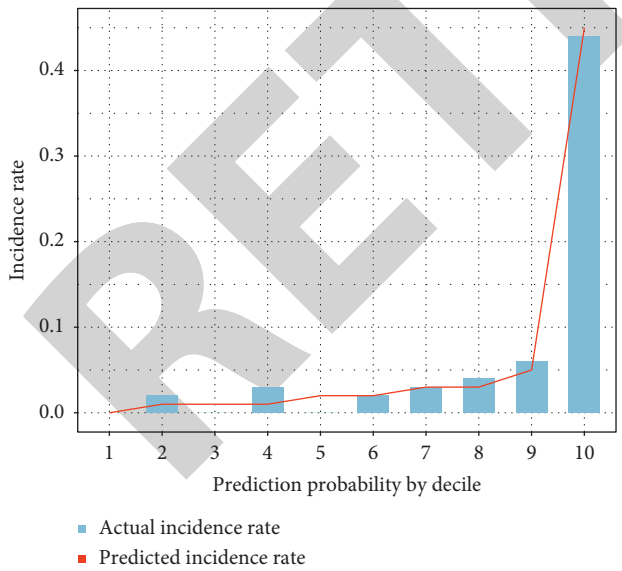

Figure 7: Distribution map of actual incidence rate and predicted incidence rate.

an independent and classical predictor of ventricular arrhythmia in patients with heart failure. It is generally believed that the changes of mechanical, morphological, electrophysiological characteristics, and neurohumoral remodeling of the heart during heart failure will not only aggravate ventricular hemodynamic disorders but also induce ventricular arrhythmias [20]. In an earlier study, Tracy et al. found that high-grade ventricular arrhythmia was associated with decreased rest and exercise LVEF, and the best predictor of ventricular arrhythmia was the decreased LVEF at rest, which worsened with exercise [21]. A number of researches had demonstrated that lower LVEF was an independent predictor of ventricular arrhythmia recurrence in CHD with secondary prevention ICD recipients [22–24]. LVEF is recognized as the gold standard of risk stratification for the occurrence of life-threatening ventricular arrhythmia. In this study, the echocardiography index LAV also entered the model. Increased LAV has been shown to be an independent risk factor for heart failure, stroke, and death. Previous studies have confirmed that enlarged LAV and impaired left atrial emptying fraction can predict the progression of heart failure and mortality [25, 26]. The hemodynamics of the left atrium and left ventricle influence and interact with each other [27]. In a retrospective study [28], Kaplan et al. found that the maximum LAV was associated with ventricular arrhythmias in patients after ICD implantation. In another study [29], Koilpillai et al. confirmed that left atrial width is related to the frequency of nonpersistent ventricular tachycardia. Similarly, in the present study, LVEF and LAV had been shown to be

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independent predictors of ventricular arrhythmias in elderly patients with CHD, and the prediction performance was improved by 28.75% after adding these two factors.

The ECG markers related to ventricular arrhythmias can reflect myocardial electrical instability, including Tp-e, Tp-e/QT, QTc, HRV, etc. The above-mentioned ECG markers reflect the heterogeneity of myocardial repolarization and plant nerve dysfunction. In recent years, studies have shown that Tp-e/QT can evaluate the time ratio of repolarization dispersion to the total duration of repolarization and can eliminate the confounding factors caused by heart rate variability and individual differences in QT intervals. So, Tp-e/QT is superior to Tp-e intervals and QT intervals and is becoming a more sensitive index for predicting ventricular arrhythmias [30–32]. In order to explore the predictability of the combination of multiple ECG parameters for ventricular arrhythmias, we added Tp-e/QT, QTcd, and HRV indicators for modeling and analysis, and it was confirmed that Tp-e/QT and QTcd could be used as independent predictors of ventricular arrhythmias in the elderly patients with CHD. In our study, the addition of ECG parameters increased the risk prediction probability of the model by 2.12%.

We also tried to identify the biomarkers to distinguish future ventricular arrhythmia risk. After univariate analysis, NT-proBNP and cTnT entered the multivariate analysis, but neither of them became independent predictors of VA. However, it cannot be denied that there is a correlation between NT-proBNP & cTnT and ventricular arrhythmias in patients with coronary heart disease. BNP and NT-proBNP have been proved to be equivalent and sensitive markers of systolic and diastolic function during left ventricular injury and can help identify high-risk groups of adverse cardiovascular events [33]. Lindholm et al. [34] confirmed that NT-proBNP and hs-cTnT had greater prognostic value than any other biomarkers for cardiovascular outcomes. In a study of ventricular arrhythmias in children, Mazurek et al. [35] found that the level of NT-proBNP increased with the severity of the ventricular arrhythmia, and the determination of NT-proBNP is helpful for the diagnosis and grading of ventricular arrhythmias.

This model is helpful for clinicians to understand important risk factors affecting VA occurrence in elderly patients with CHD so as to reduce the incidence of VA and improve the survival rate of patients. In addition, the seven indexes in the model are economical, noninvasive, and convenient and easy to obtain, with the manipulation unlimited by hospital conditions.

6. Study Limitation

Drug use had not been analyzed. The RR values of some of the seven factors in the model were close to 1, so we could not rule out the influence of drugs on the outcome and other unknown confounding factors, which could result in bias and affection on the result. In the retrospective case collection, the collection of NT-proBNP and cTnT in some cases lagged behind the event occurrence, which failed to reflect the real concentration at the event time, thus affecting the accuracy. Besides, this study was a single-center cohort evaluation, so multicenter and larger sample studies are still needed to optimize and verify the model in the future.

7. Conclusions

LVEF, LAV, QTcd, Tp-e/QT, gender, age, and HLP were independent predictors of VA risk in elderly patients with CHD. Among these factors, the echocardiology indexes LVEF and LAV had the greatest influence on the predictive efficiency of the model, followed by ECG indexes, QTcd and Tp-e/QT. After verification, the model had a good degree of differentiation and calibration, which can provide a certain reference for clinical prediction of the VA occurrence in elderly patients with CHD.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

Ying Dong and Yajun Shi are co-first authors. The funders had no role in the study design, decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors have no conflicts of interest.

Authors' Contributions

Ying Dong, Yajun Shi, Yang Li, and Xueping Wang contributed to the experiments design and data analysis. Ying Dong and Yajun Shi contributed to the data collection and manuscript writing. Miao Liu, Chengliang Yin and Rilige Wu contributed to the data analysis. Jinli Wang, Qing Dan, Ling Gao, Chenghui Zhao, Yang Mu, and Yuqi Liu contributed to the manuscript writing. All the authors contributed to the article and approved the submitted version.

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Retraction

Retracted: The Long-Term Change of Arrhythmias after Transcatheter Closure of Perimembranous Ventricular Septal Defects

Cardiology Research and Practice

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] H. Zheng, A. Lin, L. Wang, Y. Xu, and Z. Zhang, "The Long-Term Change of Arrhythmias after Transcatheter Closure of Perimembranous Ventricular Septal Defects," *Cardiology Research and Practice*, vol. 2021, Article ID 1625915, 9 pages, 2021.

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Research Article

The Long-Term Change of Arrhythmias after Transcatheter Closure of Perimembranous Ventricular Septal Defects

Hongyan Zheng,[1] **Aiwen Lin**,[1] **Li Wang**,[2] **Yukai Xu**,[3] **and Zhiwei Zhang**[3]

[1]*Department of Cardiology, Cardiovascular Institute of Panyu District, Panyu Central Hospital, No. 8 Fuyudong Rd, Guangzhou City, Guangdong Province 511400, China*
[2]*Department of Obstetrics and Gynecology, Panyu Central Hospital, No. 8 Fuyudong Rd, Guangzhou City, Guangdong Province 511400, China*
[3]*Department of Pediatric Cardiology, Guangdong Cardiovascular Institute, Guangdong General Hospital, No. 96 Dongchuan Rd, Guangzhou City, Guangdong Province 510100, China*

Correspondence should be addressed to Zhiwei Zhang; drzhangzw@sohu.com

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Objectives. To observe and analyze the long-term change of different types of arrhythmias after transcatheter closure of perimembranous ventricular septal defect (pmVSD). *Methods*. We retrospectively collected the data of patients who underwent pmVSD closure in our institution from March 2002 to December 2010. *Results*. One hundred thirty-nine patients met the inclusion criteria, of which 265 (25.5%) had early arrhythmia. They were classified into two categories: conduction abnormality (191/1039; 18.4%) and origin abnormality (94/1039; 9.0%), including 20 patients with both types of arrhythmias. The median follow-up time was 84.5 months, and 103 patients (103/191; 53.9%) with early conduction block got permanent arrhythmias, while only three patients (3/94; 3.2%) with early anomalous origin arrhythmias still had an abnormal electrocardiogram. Serious arrhythmias (28/1039; 2.7%), including II° atrioventricular block (AVB), III° AVB, and complete left bundle branch block (CLBBB), can appear immediately in the early postoperative period (21 patients) or in the late outset (seven patients) after several months or even years (6 months to 8.3 years). Twenty patients (20/21; 95.2%) with serious arrhythmia in the early postoperative period improved after early treatment, but six patients relapsed or worsened during follow-up. At the endpoint, severe arrhythmia persisted in 13 patients, of which four patients got permanent pacemaker implanted, and one patient with recurrent CLBBB died from heart failure. *Conclusions*. The probability of delayed CAVB or bundle branch block after VSD closure is low but often occurs several years after surgery. Therefore, long-term ECG follow-up should last for several years or even decades. Serious arrhythmias that appear early after transcatheter pmVSD closure may impose a risk of recurrence although they have been cured already. Close attention should be paid to the changes of cardiac function in patients with CLBBB after VSD closure, and the severity of such arrhythmia should be taken seriously and reexamined.

1. Introduction

Ventricular septal defect (VSD) is one of the most common congenital heart malformations, accounting for 40% of all congenital heart diseases [1–3], of which the majority is perimembranous VSD (pmVSD) [4]. Currently, the treatments of pmVSD mainly include interventional occluder closure and surgical repair. Compared with the surgical repair, up to now, the interventional treatments are still controversial [5]. The initial application of Amplatzer Membranous VSD Occluder was not satisfactory in the clinical practice, which prevented the promotion and application of this technology in the United States [6]. However, kinds of VSD occluders have been widely used clinically in other countries afterwards, including China [7, 8]. In order to demonstrate the safety and performance of VSD occluders in the long run, we focused on patients with at least one-year follow-up after the procedure, since many

publications only include short- or middle-term follow-up data [6, 9, 10]. Previous research has shown that the group with the AmplatzerTM Membranous and Muscular VSD occluder in child showed the highest closure rate of 93–95%, perhaps due to a better correlation between the diameter of the VSD and height of the child [11].

In China, the morbidity of complications after transcatheter pmVSD closure is decreasing in step with the increasing interventional cases [12]. Among the postoperative complications, arrhythmia happens most frequently and is the focus of most attention, especially the disturbance of conduction [11, 12]. Although it is easy to observe arrhythmias at the early postprocedures, the long-term natural process and prognosis of these operation-related arrhythmias are still uncertain.

This report described the long-term change of different types of arrhythmias in a single-center observational cohort, including 1039 consecutive patients after successful transcatheter pmVSD closure operation in Guangdong Cardiovascular Institution between 2002 and 2010 at young age, in order to find out the changing rules and risk factors of long-term arrhythmias.

2. Materials and Methods

2.1. Patient Population. Between March 2002 and December 2010, 1039 pediatric patients with pmVSD successfully underwent transcatheter device closure in Guangdong Cardiovascular Institution. Moreover, follow-up data and basic information of those patients were collected and analyzed retrospectively using medical records.

The inclusion criteria for this study included the following: (1) less than 18 years of age; (2) treatment conformed to the Chinese guideline of catheter interventional therapy for congenital heart diseases in 2004; (3) successful and safe pmVSD occluder implantation. The exclusion criteria included the following: (1) unsuccessful interventional procedure, such as the occluder not being implanted or falling off; (2) noncardiac death within one month; (3) under surgery to retrieve the occluder because of nonarrhythmias complications.

Data were collected retrospectively, including the follow-up data as well as the demographics and patients' clinical data.

2.2. Occluder and Procedure. Occluders used in this study included the Amplatzer VSD occlude (AGA Medical, Golden Valley, Minnesota), VSD Heart™ occluder (Lifetech Scientific, Shenzhen, China), and VSD Cera™ occluder (Lifetech Scientific, Shenzhen, China). The Amplatzer VSD occluder was eccentric, while the VSD Heart™ and VSD Cera™ occluder were eccentric, symmetry, or asymmetrical concentric. These devices have been described in detail in previous reports [13–15].

The perioperative protocol and procedure for transcatheter closure of pmVSD have been previously reported in detail [16]. All parents of the pediatric patients gave their written informed consent to the procedure.

2.3. Follow-Up. Clinical examination, electrocardiogram (ECG), transthoracic echocardiography (TTE), chest X-ray examination, and other examinations were performed on all subjects on the first postoperative day. The long-term outcomes of the procedure were reevaluated by ECG and TTE at 1, 3, 6, and 12 months after surgery and annually thereafter.

Postoperative arrhythmias occurring within one month were defined as early arrhythmias, while arrhythmias existing exceed one year were defined as long-term arrhythmias. Serious arrhythmias included complete atrioventricular block (CAVB), II° atrioventricular block (AVB), and complete left bundle branch block (CLBBB).

2.4. Statistical Analysis. All continuous variables are expressed as mean ± standard deviation (SD) or median with range as appropriate, and discrete variables are presented as frequencies and/or percentages. Statistical analysis was performed using SPSS for Windows Version 25 (IBM, Armonk, New York). Differences in categorical data were analyzed with the chi-square test. Multivariable analysis to study risk factors for the occurrence of arrhythmias was performed using multiple stepwise logistic regression analysis. The inclusion criterion was $p < 0.05$, while removing criterion was $p > 0.01$. All tests were two-sided. A probability value of $p < 0.05$ was considered to be statistically significant.

3. Results

3.1. Demographics and Clinical Data. One thousand thirty-nine patients were enrolled in the study. We simply divided the pmVSD into three components according to the defect location in the parasternal short-axis echo views. The inlet septum is toward between 9 and 10 o'clock, the membranous one between 10 and 11 o'clock, and the outlet one between 11 and 12 o'clock. Seventy-five patients (75/1039, 7.2%) had abnormal ECG prior to the procedure. Patients' characteristics and clinical data are described in Table 1.

3.2. Follow-Up. The termination of follow-up was December 2020, with the median duration time 84.5 months (1 month ~15 years). The follow-up rate in the first month was 97.5% (1013/1039), and the first year was 84.6% (879/1039). Eight hundred thirteen patients (78.2%) completed more than five years of follow-up.

3.3. Early Postoperative Arrhythmias. Early postoperative arrhythmias appearing in 265 patients (25.5%) were mainly divided into two categories: (1) the conduction block abnormal arrhythmias (191/1039; 18.0%), including various degrees of atrioventricular block and types of bundle branch block; (2) the origin abnormal arrhythmias (94/1039; 9.0%), including various types of premature contractions or tachycardia. There are also 20 cases of both types of arrhythmia with conduction block and abnormal origin. Arrhythmia with the highest morbidity was right bundle branch block (RBBB), including complete or incomplete

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Table 1: Demographics and clinical data.

Patients (*n*)	1039
Gender (F/M) (*n* (%))	567/472 (54.6%/45.4%)
Age at operation (years)	5.2 (1.9~17)
Age groups (n (%))	
< 5.0 years	505 (48.6%)
5.0~8.0 years	271 (26.1%)
> 8.0 years	263 (25.3%)
Weight at operation (kg)	18.0 (10~82)
VSD size (angiography) (mm)	3.6 (1.2~16.0)
pmVSD anatomy types (n (%))	
Inlet septum	315 (30.3%)
Membranous septum	674 (64.9%)
Outlet septum	50 (4.8%)
Postsurgical residual VSD (*n* (%))	16 (1.5%)
Presence of aneurysm (*n* (%))	333 (32.1%)
Procedure time (min)	80.0 (30.0~200.0).
Device size (mm)	7.0 (4~18)
Device corporation (n (%))	
AGA Medical	130
Lifetech Scientific	909
Type of device (n (%))	
Eccentric	256 (24.6%)
Symmetric concentric	593 (57.1%)
Asymmetrical concentric	190 (18.3%)

right bundle branch block, occurring in 126 patients (12.1%), followed by atrioventricular junctional tachycardia (AJT) (54/1039; 5.2%). Transient arrhythmias during procedure, minor ECG changes, such as occasion premature beats, left axis deviation, and ST segment changes were not included in this study. The incident rate of arrhythmias is described in Table 2.

Serious arrhythmias, including II° AVB, CAVB, and CLBBB, occurred in 21 patients (2.0%), of which 12 patients experienced CAVB or high-degree AVB. When severe arrhythmia, frequent premature ventricular contraction (PVC), frequent premature atrial contraction (PAC), and various types of tachycardia occurred in early postoperative period, the patients were treated with glucocorticoid (methylprednisolone 2 mg/(kg·d) or dexamethasone 0.25~0.5 mg/(kg·d)), albumin (0.5~1 g/(kg·d)), and myocardial nutrition medicine (creatinine phosphate (500~1000 mg/d)). Moreover, patients with postoperative atrioventricular block would be closely observed. When the ventricular rate was too slow, a temporary pacemaker should be installed. When the medical treatment was not effect, it might even be possible to perform an operation to remove the occluder or install a permanent pacemaker with the consent of the patient's parent. Most patients with serious arrhythmias were improved after treatment, except for one with CLBBB, without the need of permanent pacemaker installation in the early postoperative period.

3.4. Arrhythmias during Follow-Up. At the first month after the procedure, the arrhythmias morbidity dropped to 13.5% (137/1013) compared with the early rate (265/1039, 25.5%) and further decreased to 12.7% (128/1006) in the third month and 12.5% (123/977) in the sixth month. However, at the end of follow-up, the incidence rate of arrhythmias (162/879, 18.4%) increased slightly compared with the first month (18.4% vs. 13.5%; $p = 0.005$

). At the follow-up endpoint, sustained arrhythmias in 162 patients were mostly branch block (154/162, 95.1%). Long-term serious arrhythmias occurred in 14 patients, including four patients with CAVB, who underwent permanent pacemaker implantation. One patient with recurrent CLBBB had a heart failure and died at the end. The arrhythmias morbidity during the follow-up period is described in Table 2.

3.5. Long-Term Change of Different Types of Arrhythmias. The long-term change of different types of early arrhythmias after pmVSD closure is described as follows and in Table 3.

3.5.1. CAVB or High-Degree AVB. Twelve patients, including nine with persistent CAVB, two with paroxysmal CAVB, and one with high-degree AVB, were all treated with medicines such as steroid, albumin, and myocardial nutrition immediately after AVB occurred. Of 12 patients, seven received temporary pacemaker (TP) accompanied with medicine treatment. Moreover, two patients underwent surgery to remove the occluder because of poor medical treatment. All patients were improved after treatment in the early time, without the need of permanent pacemaker. During the follow-up period, three patients experienced recurrence to CAVB or II° AVB after 19 months to 46 months after the operation. In addition, six of twelve patients got worse conduction block compared with the first month. Two patients with occluder retrieved did not get AVB recurrent or conduction block aggravation. The patients who experienced AVB recurrence or conduction block aggravation during follow-up had CAVB within five days after the closure, long-term CAVB duration (≥5 days), and large occluder size (≥8 mm). The clinical data and long-term outcomes of patients with CAVB are shown in Table 4. Except for patient no. 6 that was lost to follow-up after half a year, the rest of the patients were followed up for more than five years. Patient no. 3 experienced CAVB on the sixth day after surgery and improved after two days, but on the 14th day after the operation, CAVB was observed again and a temporary pacemaker was installed. After two days, CAVB converted to CRBBB, which continued until the end of the follow-up period.

3.5.2. II° AVB. Four patients experienced a second-degree type 1 atrioventricular block in the early period. Except for one patient, which was converted to bundle branch block, all the others returned to normal ECG after medical treatment. Moreover, no recurrent or conduction block aggravation was observed during follow-up.

3.5.3. I° AVB. Thirteen patients experienced I° AVB early after the procedure, including five patients who experienced accompanying bundle branch block. Until the end of the

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Table 2: The morbidity of various types of arrhythmias during follow-up.

Arrhythmias	< 1 month ($n = 1039$)	1st month ($n = 1013$)	3rd month ($n = 1006$)	6th month ($n = 977$)	1st year ($n = 879$)	3rd year ($n = 783$)	Endpoint[1] ($n = 879$)
CAVB or high degree AVB	12 (1.2%)	0	0	0	0	1 (0.1%)	4 (0.5%)
II° AVB	4 (0.4%)	0	0	0	0	1 (0.1%)	1 (0.1%)
I° AVB + BBB	5 (0.5%)	1 (0.1%)	1 (0.1%)	2 (0.2%)	2 (0.2%)	4 (0.5%)	0
I° AVB	8 (0.8%)	2 (0.2%)	1 (0.1%)	4 (0.4%)	2 (0.2%)	1 (0.1%)	3 (0.3%)
CLBBB	5 (0.5%)	2 (0.2%)	3 (0.3%)	3 (0.3%)	5 (0.6%)	5 (0.6%)	9 (1.0%)
LAFB + RBBB	10 (1.0%)	7 (0.7%)	7 (0.7%)	9 (0.9%)	8 (0.9%)	7 (0.9%)	11 (1.3%)
LAFB	21 (2.0%)	12 (1.2%)	12 (1.2%)	13 (1.3%)	9 (1.0%)	8 (1.0%)	10 (1.1%)
CRBBB	59 (5.7%)	53 (5.2%)	46 (4.6%)	43 (4.4%)	52 (5.9%)	56 (7.1%)	64 (7.3%)
IRBBB	67 (6.4%)	54 (5.3%)	53 (5.3%)	46 (4.7%)	52 (5.9%)	40 (5.1%)	52 (6.0%)
AJT	54 (5.2%)	1 (0.1%)	2 (0.2%)	2 (0.2%)	1 (0.1%)	2 (0.3%)	3 (0.3%)
PAC or PVC	19 (1.8%)	2 (0.2%)	1 (0.1%)	0	1 (0.1%)	2 (0.3%)	0
AT or VT	21 (2.0%)	3 (0.3%)	2 (0.2%)	1 (0.1%)	3 (0.3%)	2 (0.3%)	5 (0.6%)
Total	265[2] (25.5%)	137 (13.5%)	128 (12.7%)	123 (12.5%)	135 (15.4%)	129 (16.5%)	162 (18.4%)

[1]The follow-up period should be more than one year, or it would not be included; [2]20 patients with multiple types of arrhythmias were included. CAVB: complete atrioventricular block; AVB: atrioventricular block; BBB: bundle branch block; CLBBB: complete left bundle branch block; LAFB: left anterior fascicular block; RBBB: right bundle branch block; CRBBB: complete right bundle branch block; IRBBB: incomplete right bundle branch block; AJT: atrioventricular junctional tachycardia; PAC: premature atrial contraction; PVC: premature ventricular contraction; AT: atrial tachycardia; VT: ventricular tachycardia.

Table 3: The long-term change of different types of early arrhythmias.

Early arrhythmias	Patients, n	Recovered, n (%)	Sustained, n (%)	Relieved, n (%)	Aggravated, n (%)	Recurrent, n (%)	Median time of aggravating or recurrence (range)
CAVB or high degree AVB	12	3 (25.0%)	0	6 (50.0%)	0	3 (25.0%)	46 (19 ~46) months
II° AVB	4	3 (75.0%)	0	1 (25.0%)	0	0	—
I° AVB + BBB	5	2 (40.0%)	0	3 (60.0%)	0	0	—
I° AVB	8	6 (75.0%)	1 (12.5%)	0	0	1 (12.5%)	6 months
CLBBB	5	1 (20.0%)	1 (20.0%)	0	0	3 (60.0%)	26 (6~43) months
LAFB + RBBB	10	3 (30.0%)	2 (20.0%)	4 (40.0%)	1 (10.0%)	0	—
LAFB	21	12 (57.1%)	5 (23.8%)	0	0	4[1] (19.0%)	12 (3~69) months
CRBBB	59	20 (33.9%)	22 (37.3%)	11 (18.6%)	4 (6.8%)	2 (3.4%)	9 (3~91) months
IRBBB	67	37 (55.2%)	19 (28.4%)	—	4 (6.0%)	7 (10.4%)	36 (1~79) months
AJT	54	52 (96.3%)	0	—	0	2 (3.7%)	45 (3~87) months
PAC or PVC	19	18 (94.7%)	0	—	0	1 (5.3%)	57 months
AT or VT	21	21 (100%)	0	—	0	0	—
Normal[3]	774	709 (91.6%)	—	—	65(8.4%)	—	28 (1~101) months
Total	1039[2)]	901[2] (86.7%)	50 (4.8%)	25 (2.4%)	74 (7.0%)	23 (2.2%)	32 (1~101) months

[1]Two patients returned to LAFB and the other two returned and deteriorated into LAFB + RBBB. [2]20 patients with multiple types of arrhythmias were included. [3]No new arrhythmia appeared in the early postoperative period. CAVB: complete atrioventricular block; AVB: atrioventricular block; BBB: bundle branch block; CLBBB: complete left bundle branch block; LAFB: left anterior fascicular block; RBBB: right bundle branch block; CRBBB: complete right bundle branch block; IRBBB: incomplete right bundle branch block; AJT: atrioventricular junctional tachycardia; PAC: premature atrial contraction; PVC: premature ventricular contraction; AT: atrial tachycardia; VT: ventricular tachycardia.

follow-up period, except for two patients who still experienced I° AVB, the rest of the patients had a normal ECG or relieved to bundle branch block, without worse conduction block.

3.5.4. CLBBB. CLBBB appeared in five children in the early postoperative period, and the rest experienced CLBBB within two days after the operation. After the medical treatment, one patient still experienced CLBBB, while four patients returned to normal heart rhythm in the first month after surgery. However, at the end of the follow-up period, one patient had normal ECG, and CLBBB recurred again in three patients six months to 43 months after surgery. One child (female; 2.9 years old; 18 kg) was diagnosed with inflow tract type VSD (7.7 mm) before the operation, and a VSD Heart™ occluder (eccentric type, 10 mm) was inserted during the operation. The ECG changed from normal to CLBBB on the first day after the operation and returned to normal after the medical treatment. However, CLBBB recurred at the 12th month, and the echocardiogram showed that the left ventricle enlarged with unsynchronized ventricular contraction on the 20th month. The medical treatment was not effective, and the heart failure appeared to be aggravated. Cardiac resynchronization therapy (CRT) was tried, but its effect was not good. She died of cardiogenic shock within 24 hours after the CRT pacemaker implantation.

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Table 4: Clinical data of patients with CAVB or high-degree AVB.

Patient	Age (year)	Occluder type (size)	Occurrence time postoperation (day)	Therapy	AVB duration (day)	Early conversion	Long-term conversion
1	2.7	Eccentric (6 mm)	Immediately	Medicine	1	CRBBB	LAFB + IRBBB
2	6.8	Eccentric (8 mm)	4	Medicine + TP	2	CRBBB	CRBBB
3	3.8	Eccentric (8 mm)	6; 14[1]	Medicine + TP	2; 2[1]	CRBBB	CRBBB
4	4.1	Eccentric (8 mm)	4	Medicine + TP + occluder removed	4	CRBBB	CRBBB
5	3.1	Eccentric (10 mm)	5	Medicine	3	CRBBB	CLBBB
6	10.6	Symmetric (4 mm)	6	Medicine + TP	2	Normal	Normal
7	7.9	Symmetric (10 mm)	5	Medicine + TP	5	CLBBB	CAVB
8	3.3	Symmetric (10 mm)	Immediately	Medicine	7	Normal	CRBBB
9	4.3	Symmetric (10 mm)	Immediately	Medicine + occluder removed	4	IRBBB	IRBBB
10	4.6	Eccentric (8 mm)	3	Medicine + TP	9	IRBBB	CAVB
11	3.6	Eccentric (7 mm)	6	Medicine + TP	2	IRBBB	Normal
12	7.3	Symmetric (5 mm)	2	Medicine	8	Normal	II° AVB

[1]CAVB was observed again 14 days after the operation despite of relieving at the first time. TP: temporary pacemaker.

3.5.5. Left Anterior Fascicular Block (LAFB) or LAFB + RBBB. Thirty-one patients had LAFB or LAFB + RBBB. At the end of the follow-up period, 11 patients had persistent LAFB or LAFB + RBBB, and 19 experienced a relief or disappearance of conduction block. The ECG of one patient changed from double bundle branch block to normal heart rhythm in the first month but worsened to II° AVB in the fourth year and deteriorated to CAVB at the fifth year.

3.5.6. RBBB. A total of 126 patients experienced complete right bundle branch block (CRBBB) or incomplete right bundle branch block (IRBBB). During the follow-up period, 41 patients had no significant changes in ECG, 68 patients experienced a relief if disappearance of abnormality, nine patients had a recurrent RBBB, and eight patients experienced worse conduction block (such as IRBBB aggravating to CRBBB or pure right bundle branch block aggravating to double bundle branch block (LAFB + RBBB)). Early CRBBB aggravated to CAVB in one patient in the third year after operation.

3.5.7. Origin Abnormal Arrhythmias. Origin abnormal arrhythmias include frequent premature atrial contraction (PAC), frequent premature ventricular contraction (PVC), atrioventricular junctional tachycardia (AJT), atrial tachycardia (AT) and intermittent ventricular tachycardia (VT), and so on. Due to insufficient experience in interventional therapy in the early stage, patients with these arrhythmias in the early postoperative period were treated with glucocorticoid and other drugs. With the accumulation of interventional experience, most patients with such arrhythmias did not use glucocorticoids routinely. The long-term follow-up also indicated that most of the patients (91/94; 97%) returned to sinus rhythm, and only three patients still had intermittent ectopic tachycardia during the follow-up. In all patients, no cardiac insufficiency was found during follow-up.

3.5.8. Late-Onset Arrhythmias. Of 774 patients without arrhythmia in the early postoperative period, 65 patients (65/774, 8.4%) experienced the emergence of new arrhythmias during follow-up, of which 57 experienced bundle branch block; two, I° AV; six, intermittent AJT or AT. In addition, two patients with bundle branch block in the early postoperative period developed delayed-onset CAVB in the third and fifth years of follow-up. They were treated with glucocorticoid and other drugs, but they were unable to recover and eventually received permanent pacemaker implantation. Five patients with late-onset CLBBB had normal heart rhythms in the early postoperative period, and CLBBB was dedicated six months to 8.3 years after the operation. All of them underwent cardiac echocardiography to assess the cardiac function. One of the patients had uncoordinated movement of the posterior wall of the left ventricle, but there was no clinical manifestation of heart failure and the patient is still under follow-up. The clinical data of delayed-onset severe arrhythmia after the operation is shown in Table 5.

3.6. Risk Factors. In the multivariate logistic regression model, the independent predictors of early postoperative arrhythmias are occluder size [$p = 0.09$, *OR*: 1.087/mm (95% *CI*: 1.021~1.157)], occluder type (asymmetrical concentric occluder) [$p = 0.01$, *OR*: 1.987 (95% *CI*: 1.349~2.926)], and the early operation date [$p = 0.038$, *OR*: 1.079/year (95% *CI*: 1.004~1.160)]. The independent predictors of serious arrhythmias during the early postoperative period include the age at operation [$p = 0.024$, *OR*: 0.777/year (95% *CI*: 0.624~0.967)] and early operation date [$p = 0.001$, *OR*: 1.395/year (95% *CI*: 1.146~1.697)]. In addition, we found that the independent predictors of long-term postoperative arrhythmias included the age at operation [$p = 0.006$, *OR*: 0.921/year (95% *CI*: 0.869~0.977)], occluder size [$p = 0.004$, *OR*: 1.135/mm (95% *CI*: 1.042~1.236)], pmVSD anatomy type (inlet septum) [$p = 0.024$, *OR*: 4.092 (95% *CI*: 1.209~13.854)], and operation date [$p < 0.001$, *OR*: 1.159/year (95% *CI*: 1.067~1.259)] after follow-up, and the only independent predictor of long-term serious postoperative

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Table 5: Clinical data of patients with late-onset serious arrhythmias.

Patient	Age at operation (year)	Occluder type (size)	EKG at 1st day	EKG at 1st month	EKG at 1st year	EKG at last time	The time of arrhythmia (years)
1	6.17	Eccentric (6)	Normal	Normal	Normal	CLBBB	5.74
2	3.08	Eccentric (7)	Normal	Normal	Normal	CLBBB	8.33
3	6.08	Eccentric (6)	CRBBB	CRBBB	CRBBB	CAVB	3.17
4	6.33	Asymmetrical (8)	AJT	Normal	Normal	CLBBB	7.00
5	9.17	Symmetry (8)	Normal	Normal	CLBBB	CLBBB	0.50
6	3.75	Asymmetrical (6)	Normal	Normal	CLBBB	CLBBB	0.50
7	2.42	Eccentric (8)	LAFB + IRBBB	Normal	Normal	CAVB	5.00

arrhythmias is the occluder type (eccentric occluder) [$p = 0.004$, *OR*: 1.135 (95% *CI*: 1.042~1.236)].

4. Discussion

4.1. Main Result. Arrhythmia, especially CAVB, is one of the most important complications after transcatheter occluder closure of pmVSD. The incident rate of arrhythmias in the early postoperative period ranges from 15.3% to 24.1% [12, 17], and CAVB rate ranges from 0.2% to 5.0% [8, 18–20]. However, most of the previous studies were limited to small series with insufficient follow-up, and most of the attention was toward the late-onset CAVB, ignoring the change in other arrhythmias. In this study, we emphasized the intermediate, long-term, and early postoperative arrhythmias in a sufficient number of patients and intended to evaluate the safety of transcatheter pmVSD closure in the long term.

The incident rate of early arrhythmias in this study was 20.5%, in agreement with previous reports. During the follow-up period, the rate of early arrhythmias was gradually decreasing, and half of the patients returned to normal. However, with the follow-up time extension, part of the patients may get recurrent or wore arrhythmias, especially those with serious arrhythmias.

Some scholars suggested that early postoperative CAVB could turn to normal or bundle branch block after a course of steroids [21, 22]. In this study, the early CAVB indeed changed to normal rhythm in an acute setting, but it could recur in long-term follow up. Nearly half of the patients experienced worse conduction block in the long term compared with the first month. It was suggested that steroids may only alleviate the myocardial edema and inflammation but will not solve the true reason for AVB occurrence, which is that the occluder had compressed the atrioventricular node. Affecting the conduction again is easy, once the proximal occluder displacement or deformation occurred. Similar cases have been reported accidentally [23]. Currently, there are few studies on late recurrence of CAVB. The recurrent time is difficult to predict, and it may be several months to several years after the surgery. In patients with late recurrent CAVB, medical treatment is ineffective, and permanent pacemaker seems the only choice [24]. It is worth mentioning that two patients in this study recovered after the occluder was removed, without conduction block aggravation or AVB recurrence. Therefore, it is debatable that patients with early CAVB should accept medical treatment or surgical occluder removal [25, 26]. Pacemaker insertion is usually recommended if there is no recovery from the AV conduction after one to two weeks [26, 27]. It remains unproven if steroids or other anti-inflammatory drugs increase the recovery rate of surgical CAVB [28, 29].

In this study, we found that patients with early CAVB occurrence time (≤5 days), long-term CAVB (≥5 days), and large occluder size (≥8 mm) experienced a high risk of conduction block aggravation or AVB recurrence. It may be suggested that we should remove the occluder from patients with early CAVB after ineffective medical treatment for five days.

This research also showed that patients with CLBBB experienced a high recurrence rate despite of early improvement after steroid treatment, and their cardiac function could decrease, accompanied with enlarging left ventricle. This might result from the damage of left ventricular systolic function and myocardial synchronize movement by CLBBB [30, 31]. In this study, one patient died of heart failure and another died of impaired cardiac function. Besides, other institutions in China also reported six patients with heart failure caused by CLBBB, of which two died [32]. The prognosis of this serious complication was terrible for the late-onset CLBBB with a poor response to steroid treatment. The cardiac resynchronization therapy proved to be effective in heart failure with CLBBB [33, 34], but not in this study. Therefore, further research is needed to confirm which treatment could be effective for patient with CLBBB and left ventricle enlarging.

Bundle branch block was a common complication with the highest incident rate both in the early and long-term follow-up. During follow-up, nearly half of the conduction block could return to normal, some of which could be worse or even deteriorate into CAVB. Some of the reported late-onset CAVB cases have been observed with different degrees of conduction block in the early postoperative period [35]. Although no cases with abnormal cardiac function causing by RBBB or LAFB had been observed, further studies are needed to clarify the long-term effects of LAFB or RBBB on cardiac function.

Origin abnormal arrhythmias, such as AJT, ectopic tachycardia, and ectopic premature beat, could almost disappear during follow-up and also had a rare recurrence. The underlying mechanism of these arrhythmias may be caused by the stimulation of the interventional device during

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the operation. After removing the catheters and wires in the body, the mild injury of myocardium can be improved.

Most of the patients with early rhythm in the preoperative period did not experience any change during follow-up. Some patients developed late-onset arrhythmia with an incident rate of 7.5% in this study, which is consistent with the long-term deterioration or recurrence rate of early arrhythmia (9.5%). However, this study might underestimate the incident rate of late-onset arrhythmias, because of the lower follow-up rate and shorter follow-up time compared with patients with early arrhythmias. Although most of the late-onset arrhythmias were mild ECG changes, such as RBBB, LAFB, and origin abnormality, the condition of some patients with conduction block could be worse progressively. The occurrence time could be several years or even 10 years after the operation in the study. However, now, the mechanism is uncertain. It may be relative to the inflammatory reaction or scar formation in the conduction tissue provoked by the occlude [36]. Previous research has shown that it appears to be possible that the mechanical trauma, compression, inflammation, edema, and consecutive scarring resulting in a cAVB be reduced, especially with the more flexible and softer devices [11, 37, 38].

So far, the underlying mechanism of arrhythmias after transcatheter pmVSD closure is still unclear. The risk factors may include age, weight, operation duration time, operation technique, anatomy location of the pmVSD, size of the occluder, morphological characteristics of the occluder, and so on, but the conclusions about risk factor were different in various researches [5, 12, 15, 39]. In this study, younger patients with large size occluder, asymmetrical concentric or eccentric occluder, and undergoing the operation on an early time might easily get arrhythmias. However, these risk factors have a little effect, and it is difficult to predict the probability and the exact type of arrhythmia after surgery. Some researchers even tried to use the intracardiac electrophysiology technique to predict the arrhythmias occurrence after the procedure, but the result was unsatisfying [40].

4.2. Clinical Implication. Considering the severity and unpredictability of the late-onset complications, proper early treatment and long-term careful follow-up of the postoperative arrhythmias are the key point of protecting patients from serious consequences.

It is unrealistic to monitor the ECG of every patient with pmVSD closure every month. Therefore, the timely detection of patients with high risk of late-onset serious arrhythmias is of great importance. In this study, we strongly suggest that patients with early serious arrhythmias should be under a careful and quite long-term follow-up, even though their ECG changed to normal after medical treatment.

Apart from the CAVB that have been reported repeatedly in previous research, the CLBBB, which was ignored formerly, should also be given the same attention. The consequence of the left ventricle enlargement caused by CLBBB is fatal and has no feasible treatment right now. Hence, it is mandatory to monitor the change of both ECG and cardiac ultrasound carefully and closely in patients with CLBBB. The echocardiographic color Doppler tissue imaging may be helpful when necessary [41].

4.3. Study Limitations. First, the long-term follow-up rate of patients with normal rhythm is lower than those with early arrhythmias, which raises the issue of potential bias. Second, the transient arrhythmias during interventional procedure, especially the transient AVB, were aborted in this study, because of the ignorance of operation recorder in early days. Third, it is hard to conclude the proper therapeutic protocol with statistical significance from those limited cases of serious arrhythmias. In addition, we could not summarize the rule and risk factors of the late onset arrhythmias occurring, even though we tried hard. However, the strict protocol in our institute before, during, and after the procedure made the collected data comprehensive and accurate. Lastly, the experiences of a single-center nonrandomized study may not be universally representative. Well-designed prospective cohort studies that stratify patients based on age and device type are definitely needed to establish clinical guidelines, recommending routine pmVSD transcatheter closure.

5. Conclusions

Percutaneous intervention pmVSD closure, which proved to be a safe and effective alternation, has been widely performed for decades. As time goes on, more and more long-term complications have been observed, such as late CAVB and heart failure caused by CLBBB. In spite of low incident rate, the late complications are not only more difficult to be discovered and cured than the early complications but also life threatening. Therefore, there is an urgent need to find out how to prevent and treat the interventional complications and establish a targeted long-term follow-up scheme.

Data Availability

The study is a retrospective study and the research methods adopted in the study meet the requirements of scientific research ethics. The data in the article are true and valid. The data used to support the findings of this study are included within the article and also available from the corresponding author upon request.

Additional Points

The institution at which the work was performed is Guangdong Cardiovascular Institute, Guangdong General Hospital.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Retraction

Retracted: Establishment of a Nomogram for Predicting Early Death in Viral Myocarditis

Cardiology Research and Practice

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This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope
(2) Discrepancies in the description of the research reported
(3) Discrepancies between the availability of data and the research described
(4) Inappropriate citations
(5) Incoherent, meaningless and/or irrelevant content included in the article
(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

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[1] X. Sun, N. Xie, M. Guo et al., "Establishment of a Nomogram for Predicting Early Death in Viral Myocarditis," *Cardiology Research and Practice*, vol. 2021, Article ID 9947034, 8 pages, 2021.

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Research Article

Establishment of a Nomogram for Predicting Early Death in Viral Myocarditis

Xuejun Sun,[1] Naxin Xie,[1] Mengling Guo,[2] Xuelian Qiu,[3] Hongwei Chen,[1] Haibo Liu,[1] and Hongmu Li[1]

[1]*Department of Cardiovascular Surgery, Fujian Medical University Affiliated First Quanzhou Hospital, Quanzhou, China*
[2]*Department of Medical Record, Fujian Medical University Affiliated First Quanzhou Hospital, Quanzhou, China*
[3]*Department of Pharmacy, Fujian Medical University Affiliated First Quanzhou Hospital, Quanzhou, China*

Correspondence should be addressed to Haibo Liu; lhb2233.hot@163.com and Hongmu Li; lihm25@mail3.sysu.edu.cn

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Objective. This research aimed to establish a nomogram for predicting early death in viral myocarditis (VMC) patients. *Method*. A total of 362 consecutive VMC patients in Fujian Medical University Affiliated First Quanzhou Hospital between January 1, 2009, and December 31, 2019, were included. A least absolute shrinkage and selection operator (LASSO) regression model was used to detect the risk factors that most consistently and correctly predicted early death in VMC. The performance of the nomogram was assessed by calibration, discrimination, and clinical utility. *Result*. 9 factors were screened by LASSO regression analysis for predicting the early death of VMC. Combined with the actual clinical situation, the heart failure (HF) (OR: 2.13, 95% CI: 2.76–5.95), electrocardiogram (ECG) (OR: 6.11, 95% CI: 1.05–8.66), pneumonia (OR: 3.62, 95% CI: 1.43–9.85), brain natriuretic peptide (BNP) (OR: 4.66, 95% CI: 3.07–24.06), and lactate dehydrogenase (LDH) (OR: 1.90, 95% CI: 0.19–9.39) were finally used to construct the nomogram. The nomogram's C-index was 0.908 in the training cohort and 0.924 in the validation cohort. And the area under the receiver operating characteristic curve of the nomogram was 0.91 in the training cohort and 0.924 in the validating cohort. Decision curve analysis (DCA) also showed that the nomogram was clinically useful. *Conclusion*. This nomogram achieved an good prediction of the risk of early death in VMC patients.

1. Introduction

Viral myocarditis (VMC) is one of the common clinical cardiovascular diseases, which is caused by viral infection, especially the localized or diffuse myocardial inflammatory lesions caused by Coxsackie B virus [1]. The potential pathogenesis was considered to be that the virus-mediated immune response can directly act on cardiomyocytes and intracardiac capillaries, leading to degeneration and necrosis of cardiomyocytes and ultimately injury cardiac dysfunction [2, 3]. The prognosis of most cases is good, but a small number of patients can have an acute outbreak leading to heart failure or sudden death, a small number of patients keep the heart cavity enlarged for several months to several years without heart failure, or the condition deteriorates again and evolves into dilated myocarditis [4, 5].

At present, there is no uniform standard for the diagnosis of viral myocarditis. Due to the lack of specificity in the clinical manifestations of viral myocarditis and most auxiliary examinations, the pathogenesis is not fully understood and the treatment is not satisfactory [6, 7]. There are no effective and safe preventive measures against early death from viral myocarditis. Therefore, accurate prognostic assessment will help doctors understand the early death risk of patients with viral myocarditis and take timely intervention measures to increase the survival probability of patients. However, there is no predictive model with good predictive ability for early death in VMC patients till now.

In this study, we retrospectively analyzed the existing case data to find the key factors for early death of viral myocarditis, build a nomogram to evaluate the severity of the patient's condition at the time of admission, and adopt corresponding treatment methods to reduce early death.

2. Patients and Methods

2.1. Patients. The study was approved by the Ethics Committee of Quanzhou First Hospital Affiliated to Fujian Medical University. A total of 362 consecutive hospitalizations of patients who were clinically diagnosed with VMC from January 1, 2009, to December 31, 2019, were included. The patients included in the study must be finally diagnosed with VMC, referring to the diagnostic guidelines of the Chinese Medical Association [8, 9], and the case data are complete. According to the clinical outcome at the time of discharge, they are divided into the survival group and death group (Figure 1).

2.2. Statistical Analysis. All statistical analysis was performed with R Studio software (Version 3.6.3, https://rstudio.com/). The least absolute shrinkage and selection operator (LASSO) regression method was used to detect the related risk factors in VMC [10, 11]. The "rms" package for *R* was used to make the nomogram. The accuracy of the nomogram was assessed by the discrimination ability and the calibration plot in the training set and the validating set [12]. AUC of receiver operating characteristic (ROC) was used to evaluate the discrimination ability of the nomogram. Decision curve analysis (DCA) was performed to evaluate the clinical utility of the nomogram [13, 14]. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

3. Result

3.1. Training Cohort's Characteristics. A total of 362 VMC patients visiting our clinic from January 1, 2009, to December 31, 2019, were assigned to training cohort. According to the principle of random allocation, 254 cases were screened for eligibility as the training cohort. Another 94 patients were enrolled into as validation cohort. There was no significant difference in demographic and clinical characteristics between the two groups, as given in Table 1.

3.2. Selection of Predictors for Early Death in VMC Patients. LASSO regression analyzed was performed to reduce 26 variables to 9 potential predictors in the training cohort (Figures 2(a) and 2(b)). However, only 5 predictors were enrolled into nomogram after combined with the actual clinical situation, including HF (OR: 2.13, 95% CI: 2.76–5.95), ECG (OR: 6.11, 95% CI: 1.05–8.66), pneumonia (OR: 3.62, 95% CI: 1.43–9.85), BNP (OR: 4.66, 95% CI: 3.07–24.06), and LDH (OR: 1.90, 95% CI: 0.19–9.39). The results of multivariate logistic analysis are presented in Table 2.

3.3. Nomogram Construction and Performance. A nomogram was constructed for predicting early death in VMC patients (Figure 3). Validation of the nomogram was performed with a 1000 bootstrap analysis. Harrell's concordance index was 0.908 in the training cohort and 0.924 in the validation cohort. The calibration curves of the nomogram showed good probability consistencies between the prediction and observation in the training cohort and validating cohort (Figures 4(a) and 4(b)). The area under ROC curve of the probability of early death was 0.91 in the training cohort and 0.92 in the validating cohort (Figures 4(c) and 4(d)).

3.4. Clinical Utility of the Nomogram. Decision curve analysis (DCA) was used to evaluate the clinical value of the nomogram using the data from all 362 patients. The DCA curve for the predictive nomogram is shown in Figure 5, which shows that when the nomogram-predicted probability of early death was <66%, the nomogram provided additional value relative to the treat-all-patients scheme or the treat-none scheme, suggesting that the nomogram was clinically useful.

4. Discussion

Viral myocarditis (VMC) is caused by various viruses infecting the myocardium, most of which have a good prognosis [3]. However, it has been linked as the cause of sudden cardiac death in young adults in up to 12% of cases [15, 16]. Little is known about the early stages of VMC in humans currently [7, 17]. There is no model with good predictive ability for early death in VMC patients till now.

In the present study, a nomogram was established to predict early death based on the clinical features of patients with VMC. 5 predictors were used to establish the nomogram, which included HF, ECG, pneumonia, BNP, and LDH. Finally, the nomogram provided good discrimination and calibration values, which may help to timely intervene in patients with VMC who are at high risk of early death.

HF is a consequence of various cardiovascular diseases, always associated with poor prognosis [18]. In this study, VMC patients with heart failure had a higher probability of early death. In addition, abnormal ECG is a strong prognostic indicator in the nomogram. However, Dec et al. suggested that ECG findings are neither sensitive nor specific for the diagnosis of myocarditis [19], which requires further exploration.

Zhang et al. [20] suggested that levels of brain natriuretic peptide (BNP) measured in the plasma could be a useful biochemical marker for the myocarditis, and high concentration of BNP may correlate with poor prognosis in patients with myocarditis. Thus, pneumonia and LDH elevated seemed to be an important sign of early death in VMC patients. However, no correlation with prognosis was found in previous studies.

In this study, the levels of CK, CK_MB, and TNI_I were not significant for early death. However, a significant increase in TNI_I may suggest a worse prognosis [21].

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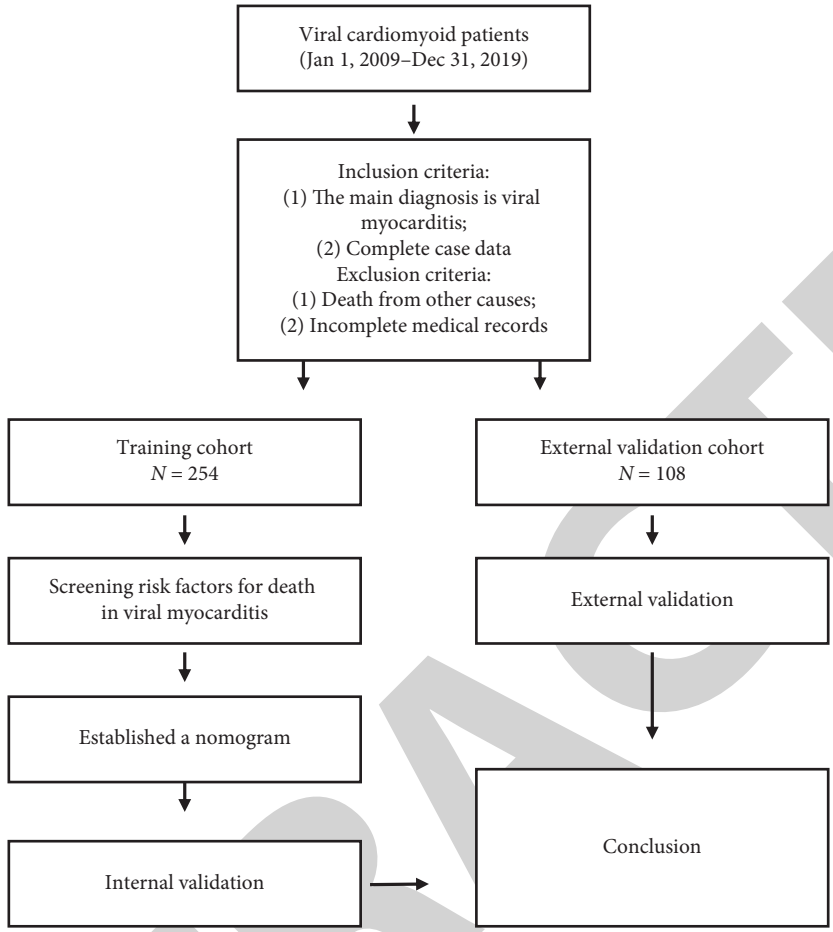

Figure 1: Research plan and implementation flow chart.

Table 1: Demographic and clinical characteristics of all patients.

Variables	Training cohort ($n = 254$)		Validation cohort ($n = 108$)		P value
	Early death (25)	Survival (229)	Early death (10)	Survival (98)	
Age (>60 y)	16 (64.00)	154 (67.25)	8 (80.00)	67 (68.37)	>0.05
Male	15 (60.00)	143 (62.44)	4 (40.00)	60 (61.22)	>0.05
Smoking	5 (20.00)	34 (14.85)	0 (0.00)	21 (21.43)	<0.05
Drinking	17 (68.00)	175 (76.42)	8 (80.00)	67 (68.37)	>0.05
Hypertension	1 (4.00)	16 (9.99)	1 (10.00)	5 (5.10)	>0.05
Diabetes	0 (0.00)	5 (2.18)	1 (10.00)	2 (2.04)	>0.05
HF	9 (37.04)	25 (10.92)	4 (40.00)	8 (8.16)	>0.05
Abnormal ECG	10 (40.00)	180 (78.60)	10 (100.00)	17 (17.35)	<0.05
Pneumonia	17 (68.00)	55 (24.02)	8 (80.00)	25 (25.51)	>0.05
WBC (>9.5 × 10^9/L)	16 (64.00)	103 (44.98)	10 (100.00)	49 (50.00)	>0.05
N% (>75%)	20 (80.00)	100 (43.67)	8 (80.00)	48 (48.98)	>0.05
Lymphocyte >3.2 × 10^9/L	7 (28.00)	9 (3.93)	2 (20.00)	6 (6.12)	>0.05
Monocyte >0.6 × 10^9/L	11 (44.00)	51 (22.27)	3 (30.00)	28 (28.57)	>0.05
Hb < 120 g/L	6 (24.00)	30 (13.10)	0 (0.00)	12 (12.24)	>0.05
PLT <100 × 10^9/L	8 (32.00)	29 (12.66)	5 (50.00)	24 (24.49)	>0.05
BNP ≥500 pg/L	24 (96.00)	80 (34.93)	9 (90.00)	36 (36.73)	>0.05
TNI_I > 0.5 ng/ml	23 (92.00)	140 (61.14)	8 (80.00)	65 (66.33)	>0.05
TP < 65 g/L	6 (24.00)	10 (4.37)	2 (20.00)	3 (3.06)	>0.05
Albumin<40 g/L	4 (16.00)	28 (12.23)	3 (30.00)	8 (8.16)	>0.05
ALT >50 U/L	19 (76.00)	101 (44.10)	7 (70.00)	42 (42.86)	>0.05
AST >40 U/L	22 (88.00)	110 (48.03)	7 (70.00)	50 (51.02)	>0.05
LDH ≥300 U/L	24 (96.00)	110 (48.03)	8 (80.00)	55 (56.12)	>0.05

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Table 1: Continued.

Variables	Training cohort ($n = 254$)		Validation cohort ($n = 108$)		P value
	Early death (25)	Survival (229)	Early death (10)	Survival (98)	
CK > 200 U/L	25 (100.00)	193 (85.77)	8 (80.00)	87 (88.78)	>0.05
CK_MB > 25 U/L	23 (92.00)	146 (63.76)	7 (70.00)	70 (71.43)	>0.05
Cr ≥110 umol/L	11 (44.00)	28 (12.22)	6 (60.00)	10 (10.20)	>0.05
UA >500 umol/L	10 (40.00)	67 (29.26)	6 (60.00)	20 (20.41)	>0.05

HF, heart failure; ECG, electrocardiogram; WBC, white blood cell count; *N*%, neutrophil percentage; Hb, hemoglobin; PLT, platelet; BNP, brain natriuretic peptide; TP, total protein; TNI_I, Troponin I; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase, MB form; Cr, creatinine; UA, uric acid.

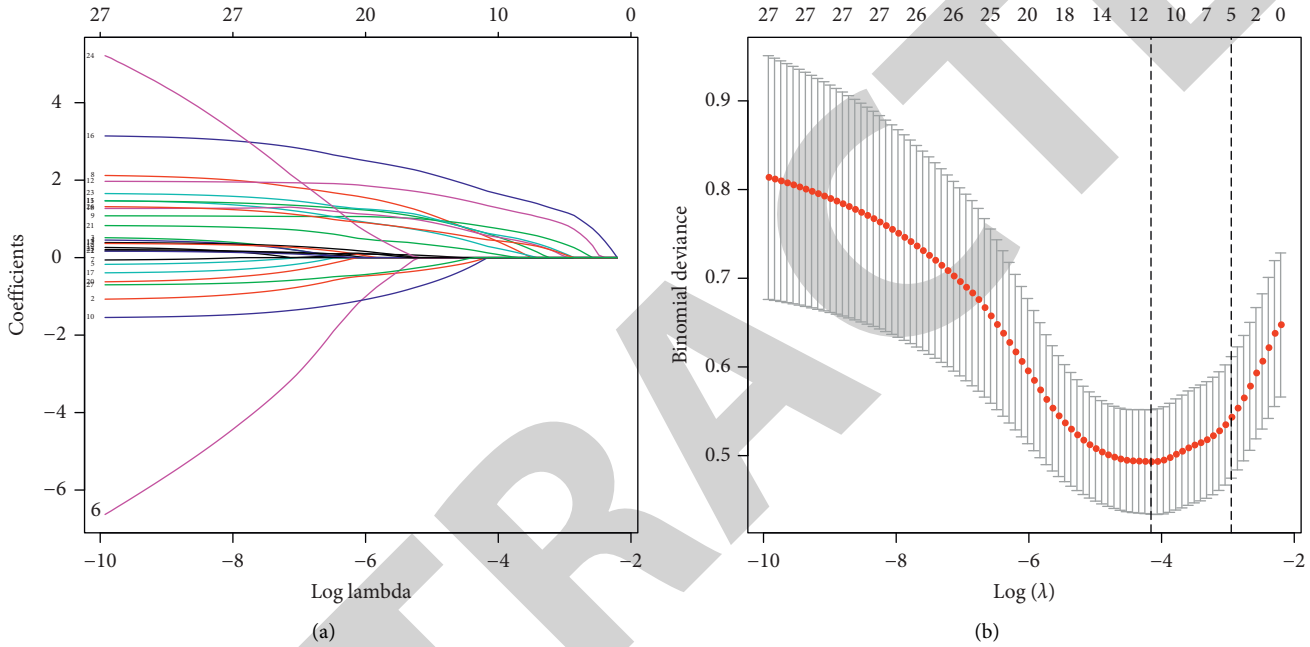

Figure 2: Lasso regression analysis was used to screen the potential predictors. (a) The results without cross-validation. (b) The results after cross-validation.

Table 2: Prediction factors for early death in VMC patients.

Intercept and variable	Prediction model		
	β	Odds ratio (95% CI)	P value
Intercept	−8.52	0.04 (95% CI:0.00–0.16)	$P < 0.05$
HF	0.45	1.57 (95% CI:1.86–4.73)	$P > 0.05$
ECG (abnormal)	2.14	8.49 (95% CI:1.42–12.34)	$P > 0.05$
Pneumonia	1.14	3.11 (95% CI:1.14–9.02)	$P < 0.05$
BNP (≥ 500 pg/L)	2.68	3.97 (95% CI:2.70–20.10)	$P < 0.05$
LDH (≥ 300 U/L)	0.63	1.87 (95% CI:2.45–5.22)	$P > 0.05$

HF, heart failure; ECG, electrocardiogram; BNP, brain natriuretic peptide; LDH, lactate dehydrogenase.

There are also several limitations of this research. First, this study was dependent on the data of a single institutional cohort of patients from the Asia-Pacific region. Second, this retrospective study was susceptible to certain biases that could not be completely avoided. Third, in medical practice, instead of applying endomyocardial biopsy (EMB), the

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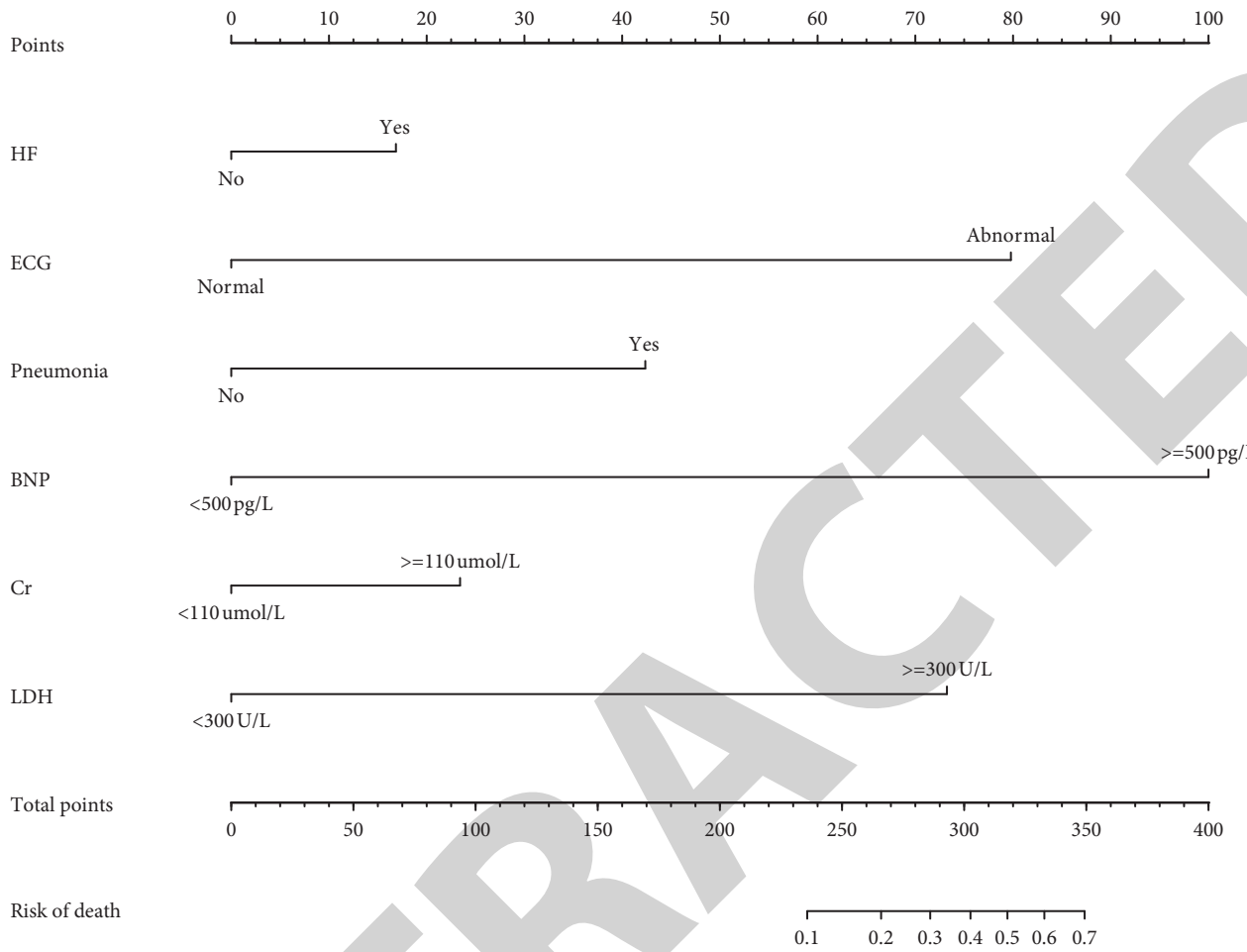

Figure 3: The nomogram for preoperative prediction of early death in viral myocarditis (VMC) patients.

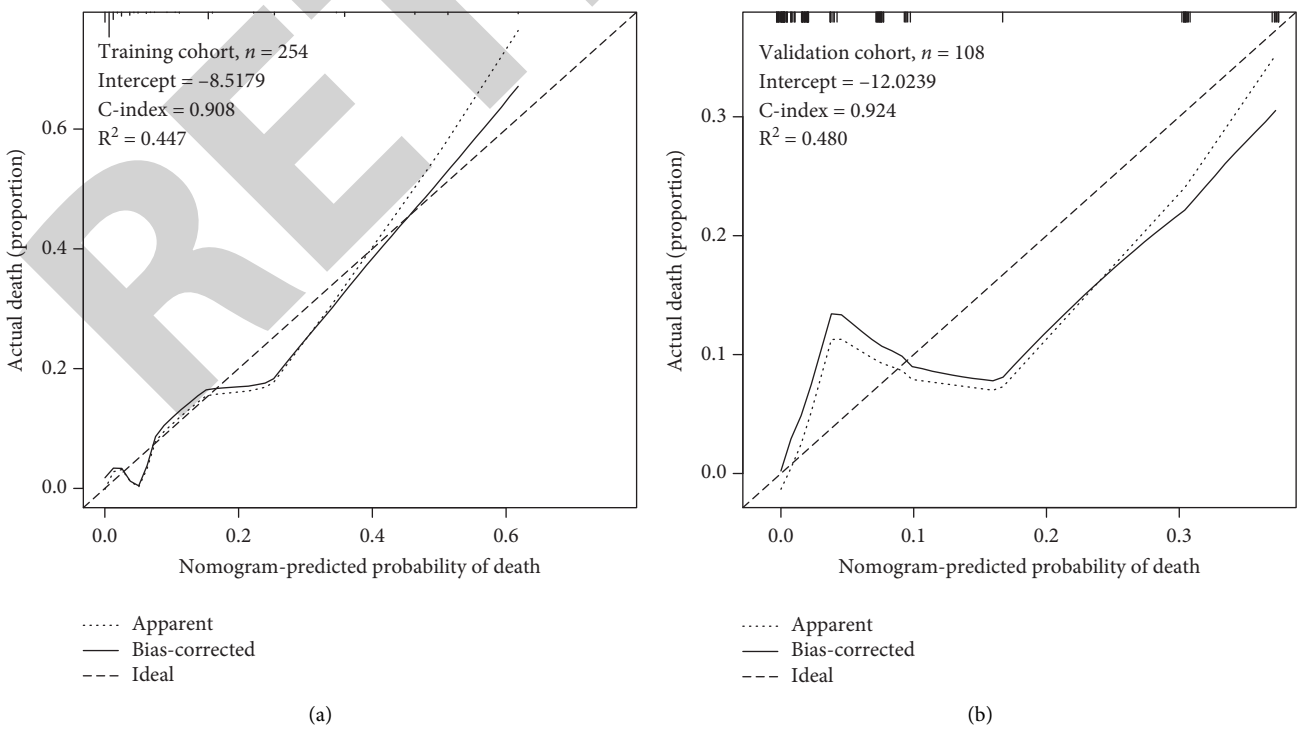

Figure 4: Continued.

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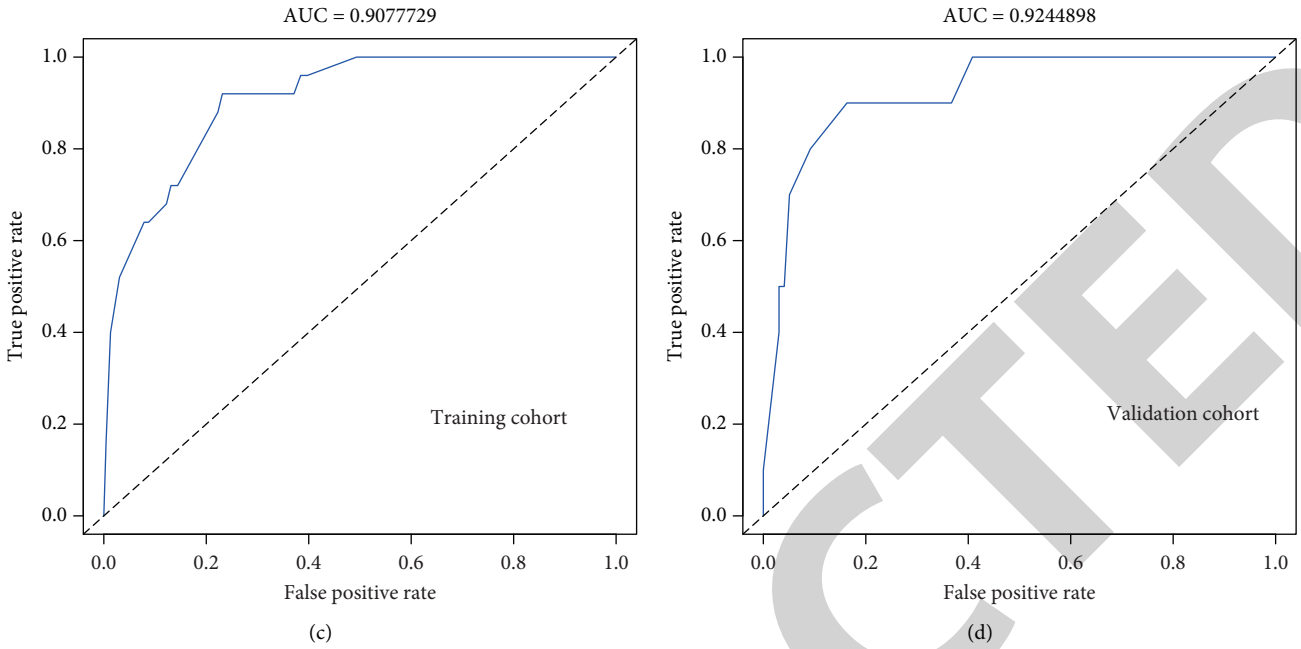

Figure 4: The performance of the nomogram. Calibration plot of the nomogram in (a) the training cohort and (b) validation cohort. The receiver operating characteristic (ROC) curves of the nomogram in (c) the training cohort and (d) the validation cohort.

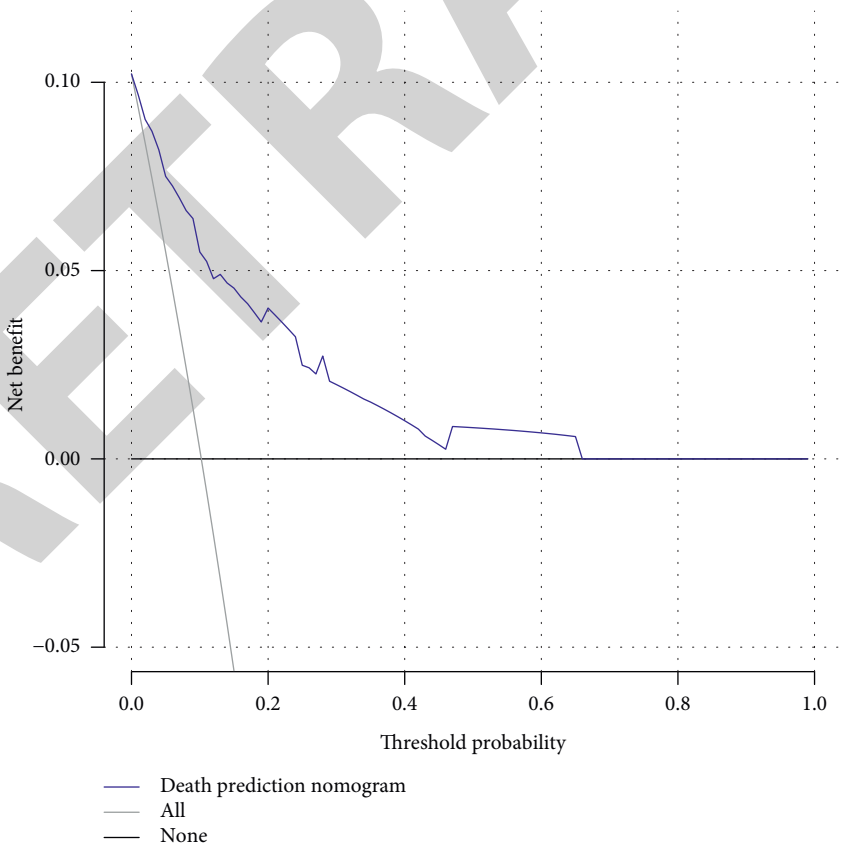

Figure 5: Decision curve analysis for the nomogram.

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current gold standard for diagnosis [22], physicians rely on a combination of clinical features, laboratory analyses, and imaging to diagnosis VMC.

5. Conclusion

In conclusion, we established and validated a nomogram for predicting early death in VMC patients. The nomogram has an adequate ability of discrimination, calibration, and may be a valuable tool for clinical practice.

Data Availability

The data used to support the findings of this study are included within the article and within the supplementary files.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Xuejun Sun and Naxin Xie contributed equally to this work. Xuejun Sun, Haibo Liu, and Hongmu Li contributed to the study design. Xuejun Sun, Naxin Xie, Mengling Guo, Hongwei Chen, and Xuelian Qiu contributed to literature search. Mengling Guo and Xuelian Qiu contributed to collect data. Xuejun Sun and Naxin Xie wrote the article and performed data analysis. Haibo Liu and Hongmu Li contributed to edit, supervision, and funding acquisition. All authors gave the final approval of the version to be submitted.

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Supplementary Materials

Supplementary Table 1. Original data of training cohort. Supplementary Table 2. Original data of validation cohort. Supplementary Table 3. Original script. (*Supplementary Materials*)

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